October 31, 2001
NRA 01-OBPR-07
OMB Approval No. 2700-0087

National Aeronautics and Space Administration
Office of Biological and Physical Research
Washington, DC 20546-0001

NASA Research Announcement Soliciting Research Proposals

Multiple Opportunities for Ground-Based Research in Space Life Sciences

1. **Biomedical Research & Countermeasures Program & Advanced Human Support Technology Program (Space Human Factors Engineering Element)**

2. **National Space Biomedical Research Institute**

3. **Countermeasure Evaluation and Validation Project**

A Research Announcement for the
NASA Office of Biological and Physical Research

Notices of Intent Due: November 30, 2001
Proposals Due: January 31, 2002

TABLE OF CONTENTS

NASA Research Announcement
Summary and Supplemental Information

Multiple Opportunities for Ground-Based Research in Space Life Sciences
NRA 01-OBPR-07

1. **Biomedical Research & Countermeasures Program and Advanced Human Support Technology Program**
   (Space Human Factors Engineering element)
2. **National Space Biomedical Research Institute**
3. **Countermeasure Evaluation and Validation Project**

This National Aeronautics and Space Administration (NASA) Research Announcement (NRA) solicits proposals for ground-based research in Space Life Sciences through three distinct opportunities. Applicants must: 1) determine which opportunity is best suited for their research project, 2) clearly identify which one of the three opportunities they are applying to (**do not submit the same research proposal to more than one opportunity**), and 3) follow the specific application procedures for the selected opportunity by referring to the appropriate Appendix. The following guidance should be used in determining the appropriate opportunity:

1. **Investigators submitting individual, independent projects** to the Biomedical Research & Countermeasures (BR&C) Program or the Space Human Factors Engineering (SHFE) element of the Advanced Human Support Technology (AHST) Program should refer to **Appendix B**;

2. Investigators who wish to become **members of an existing team of NASA's National Space Biomedical Research Institute (NSBRI)** should refer to **Appendix C**; and

3. Investigators who wish to propose testing a **proven biomedical countermeasure for use on the International Space Station using a bed rest microgravity model** through the NASA Johnson Space Center (JSC) Countermeasure Evaluation and Validation Program (CEVP) should refer to **Appendix D**.

Applicants are encouraged to refer to Figure 1 on page A-4 of this NRA to help determine what Countermeasure Readiness Level (CRL) their project addresses.

NASA investigators use the space environment to increase knowledge of biological and medical processes, to provide the biomedical foundation in support of the International Space Station and exploration beyond low Earth orbit, and to enrich life on Earth through the transfer of new space technology, medicine, and fundamental knowledge. This research supports NASA's mission through the Office of Biological and Physical Research (OBPR). All respondents to this NRA are strongly encouraged to promote general scientific literacy and public understanding of life sciences, the space environment, and the OBPR programs through formal and informal education

opportunities. Where appropriate, supported investigators will be required to produce, in collaboration with NASA, a plan for communicating their work to the public.

In this NRA

- Appendix A provides an introduction and overview to the goals, objectives and implementation strategies of the OBPR.
- Appendices B, C, and D contain descriptions of the three opportunities, instructions for submitting a notice of intent (NOI) to submit a proposal, and instructions for proposal submission.
- Appendix E contains the "Instructions for Responding to NASA Research NRAs for Solicited Research Proposals."

Proposals submitted in response to this NRA must address the research emphases described in this announcement. Those that do not will be returned. **This NRA does not solicit flight research**. Other NRAs calling for focused research or utilization of unique resources may be issued throughout the year.

Proposals selected by NASA will be funded as grants incrementally for activities lasting up to four years, pending satisfactory progress. Proposals selected by the NSBRI will be funded as subawards by the NSBRI for activities lasting up to four years. The funding duration will depend on proposal requirements, review panel recommendations, and continuing progress of the activity. All proposals will be evaluated for overall scientific and technical merit by independent peer review panels. Relevance to NASA's programmatic needs and goals will be evaluated by NASA. Relevance to NSBRI's programmatic needs and goals will be evaluated separately by the NSBRI. Final selection will be coordinated between the Bioastronautics Research Division at NASA Headquarters and the NSBRI to ensure programmatic balance and elimination of duplicate efforts. Funds are not currently available for awards under this NRA. The government's obligation to make award(s) is contingent upon the availability of appropriated funds from which payment can be made and the receipt of proposals that the government determines are acceptable for award under this NRA. The total annual cost for ground research cannot exceed $400,000. Costs in excess of this limit will require strong and extensive justification. NASA and the NSBRI do not provide separate funding for direct and indirect costs; thus, the amount of the award requested is the total of all costs submitted in the proposed budget. It is planned for selections to be announced by June 30, 2002, and awarded shortly thereafter.

Inclusion of Women and Minorities in Research Involving Human Subjects – NASA and the NSBRI have adopted the NIH policy regarding this matter. Women and members of minority groups and their subpopulations must be included in NASA-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

Participation in this NRA is open to all categories of United States (U.S.) organizations, industry, educational institutions, other nonprofit organizations, NASA laboratories, and other agencies of the U.S. government. In order to be reviewed, individual ground-based proposals responding

according to the instructions in Appendix B must be from U.S. entities or from non-U.S. entities that involve substantive co-investigator collaboration from an U.S. entity. NASA will not fund non-U.S. entities. The NSBRI accepts and reviews proposals from foreign applicants, but potential foreign applicants should note that, normally, the country of origin, not the NSBRI, must fund projects from non-U.S. organizations. CEVP proposals submitted from international member states of the International Space Life Sciences Working Group will be reviewed, but the proposal must be approved for funding by the space agency of the member country.

A notice of intent (NOI) to propose is requested by November 30, 2001. Proposals must be submitted by January 31, 2002, 5:00 PM Eastern Time. (see Appendices B, C, and D of this NRA for specific instructions for these activities.

The following items apply only to this NRA:

Solicitation NRA Identifier:	NRA 01-OBPR-07
Number of Copies Required:	Original + 20 copies for the non-NSBRI submissions; Electronic proposals for the NSBRI submissions
Notices of Intent Due:	November 30, 2001
Proposals Due:	January 31, 2002
Selection Announcement:	June 30, 2002
Funding Begins:	Approximately 30-90 days following notification of selection
Selecting Officials:	For Individual BR&C, AHST, and CEVP proposals: Director, Bioastronautics Research Division, Office of Biological and Physical Research, NASA Headquarters For NSBRI proposals: Director, National Space Biomedical Research Institute

Additional information about the BR&C, AHST, and CEVP Programs is available from

David L. Tomko, Ph.D.
NASA Headquarters, Code UB
Washington, DC 20546-0001
Telephone: 202-358-2211
Fax: 202-358-4168
Email: dtomko@hq.nasa.gov

Information about the NSBRI is available from

Ronald J. White, Ph.D.
National Space Biomedical Research Institute
One Baylor Plaza, NA-425
Houston, TX 77030-3498

Telephone: 713-798-7412
Fax: 713-798-7413
Email: rwhite@bcm.tmc.edu

Grants Office points of contact will be identified in selection letters. The NRA will be updated and issued annually and is NASA's primary means of obtaining research proposals from the life sciences community. This NRA is restricted to the programs named above and described in detail in the Appendices. Potential investigators should read with care the program descriptions that are of interest, and focus their proposals on the specific research emphases defined in this NRA.

Your interest and cooperation in participating in this effort is appreciated.

Original Signed by

Kathie L. Olsen, Ph.D.
Acting Associate Administrator
Office for Biological and Physical Research

APPENDIX A
NRA 01-OBPR-07

Background Information

Multiple Opportunities for Ground-Based Research in Space Life Sciences

I. Introduction

This NASA Research Announcement (NRA) is a consolidated NASA solicitation for research proposals in support of the NASA Office of Biological and Physical Research (OBPR) goals and objectives. Research is solicited for conduct by the Biomedical Research & Countermeasures (BR&C) Program, the Space Human Factors Engineering (SHFE) element of the Advanced Human Support Technology (AHST) Program, the National Space Biomedical Research Institute (NSBRI), and the Countermeasure Evaluation and Validation (CEVP) Project at the NASA Johnson Space Center.

The major goals of NASA's Office of Biological and Physical Research are to

- enable exploration by conducting research to enable safe and productive human habitation of space;
- use the space environment as a laboratory to test the fundamental principles of physics, chemistry, and biology;
- enable and promote commercial research in space; and
- use space research opportunities to improve academic achievement and the quality of life.

The BR&C Program is responsible for research to develop practical health-related methods for the prevention, diagnosis, treatment, and/or rehabilitation of space crews who live and work in microgravity.

The SHFE element within the AHST Program has the mission of creating and maintaining a safe and productive environment for humans in space. With space missions absorbing new technologies at an ever-increasing rate, it is imperative that planners insure that these advances will enhance crew performance without increasing stress or risk. The SHFE element is an interdisciplinary effort covering all aspects and facets of the general discipline of human factors engineering and sharing selected aspects of the behavior and performance discipline of the BR&C Program. The SHFE element encompasses a broad range of activities from basic research to development of state-of-the-art tools for measuring human performance, to applying those tools to solve operational human/system interface issues in human space flight programs. Development of new technologies and conceptual designs for flight crew accommodations needed for human missions beyond low earth orbit is also considered the responsibility of the SHFE element.

The NSBRI is a NASA-initiated and -funded private, non-profit research consortium charged by NASA with developing biomedical countermeasures for potential health problems that could occur in astronauts either during long-duration space flight or on their return to Earth. The NSBRI's current program consists of nearly 90 research and technology projects in twelve research areas.

The goal of the CEVP is to systematically and scientifically evaluate and validate terrestrial proven biomedical candidate countermeasures for space flight use that have reached a high degree of maturity. Candidate countermeasures will first be evaluated experimentally using ground-based analogs of space flight. A candidate countermeasure's targeted effects will be assessed, its side effects defined, and its interactions with other countermeasures identified. After evaluation, a candidate countermeasure may be validated in systematic experiments during actual space flight to assess those same factors. The CEVP functions using a team approach, in which the investigator becomes a member of a team that integrates space medicine and space research expertise resident inside and outside of the Agency. This team is coordinated by the NASA Johnson Space Center (JSC). The CEVP is the final step in a process in which ideas and concepts emerging from basic research are developed into operational countermeasures that are turned over by researchers to be implemented as part of NASA's mission operations.

The BR&C Program, the NSBRI, the SHFE element of the AHST Program, and the CEVP share scientific and educational goals to fund research that will result in the delivery of health-related countermeasures for astronauts. NASA is committed to maintaining a strong, openly competitive, peer-reviewed research program. Opportunities for investigators that are covered by this NRA include individual investigator awards (directly through BR&C & AHST Programs), participation in focussed discipline team research (NSBRI), and systematic experiments to evaluate and validate potential countermeasures (CEVP). Investigators should apply through whichever of these mechanisms is most suitable to enable them to conduct research in support of NASA's OBPR Programs. ***It is critical for investigators to read carefully all of the instructions in this NRA. All proposals will undergo peer-review using the same processes and procedures, but procedures and forms for proposal submission differ for the different programs and elements, and the eventual funding of selected proposals will differ for the different types of awards.*** Programmatic balance is maintained by the selecting official(s) for the program.

The research programs described in this NRA support the utilization of specialized NASA ground-based facilities and the development of special technologies required in the pursuit of its research goals. Investigators can access NASA specialized ground-based facilities for their research. Please refer to the *Space Life Sciences Ground Facilities Information Package* for instructions on how to incorporate the use of these facilities into a proposal:
http://research.hq.nasa.gov/code_u_nra/current/NRA-01-OBPR-07/index.html

This and the following Appendices define the research program and elements encompassed by this NRA, describe the specific areas of ground-based research that proposals should address, and describe the specific emphases that are acceptable for submission in response to this NRA. **This NRA does not request proposals for flight research**. It is important that the prospective investigator read the relevant section(s) carefully, as many of the programmatic emphases are

different from those appearing in previous NRAs. In addition, each Appendix includes guidelines, requirements, and instructions for preparing and submitting proposals, and defines the administrative policies governing the programs and applicants to the particular component described in this NRA.

II. Critical Path Roadmap

In order to identify and make publicly known the biomedical risks of space flight and the research questions that must be answered to reduce those risks, NASA has developed the Critical Path Roadmap (CPR). The CPR is an interdisciplinary tool to assess, understand, mitigate, and manage the risks associated with long-term exposure to the space environment. It assumes an overarching strategy that integrates requirements, risks, risk factors, critical questions, tasks, deliverables, and risk mitigation with the intent of directing biomedical research in support of human space flight, especially human missions of exploration. **Each investigator must examine and understand the CPR, and specify in their proposal which critical questions their proposed research will answer.**

The CPR is based in part on recommendations from internal NASA experts, NSBRI scientists, advisory committees, task forces, and published reports such as the National Research Council (NRC) Space Studies Board's "A Strategy for Research in Space Biology and Medicine in the New Century," the Aerospace Medical Advisory Committee, the NASA Task Force on Countermeasures, the International Space Life Sciences Working Groups publications on Radiation, Bone, Muscle, Cardiovascular, Human Factors, and Neuroscience Workshops; and the NASA Medical Policy Board Document.

The ultimate goal of the CPR is to protect the health and safety of space flight crews by allowing NASA and the community of scientists to better define and focus the research that is required for development and validation of operational health care "deliverables" for the prevention, treatment and rehabilitation of space flight changes and of appropriate habitation and medical care systems.

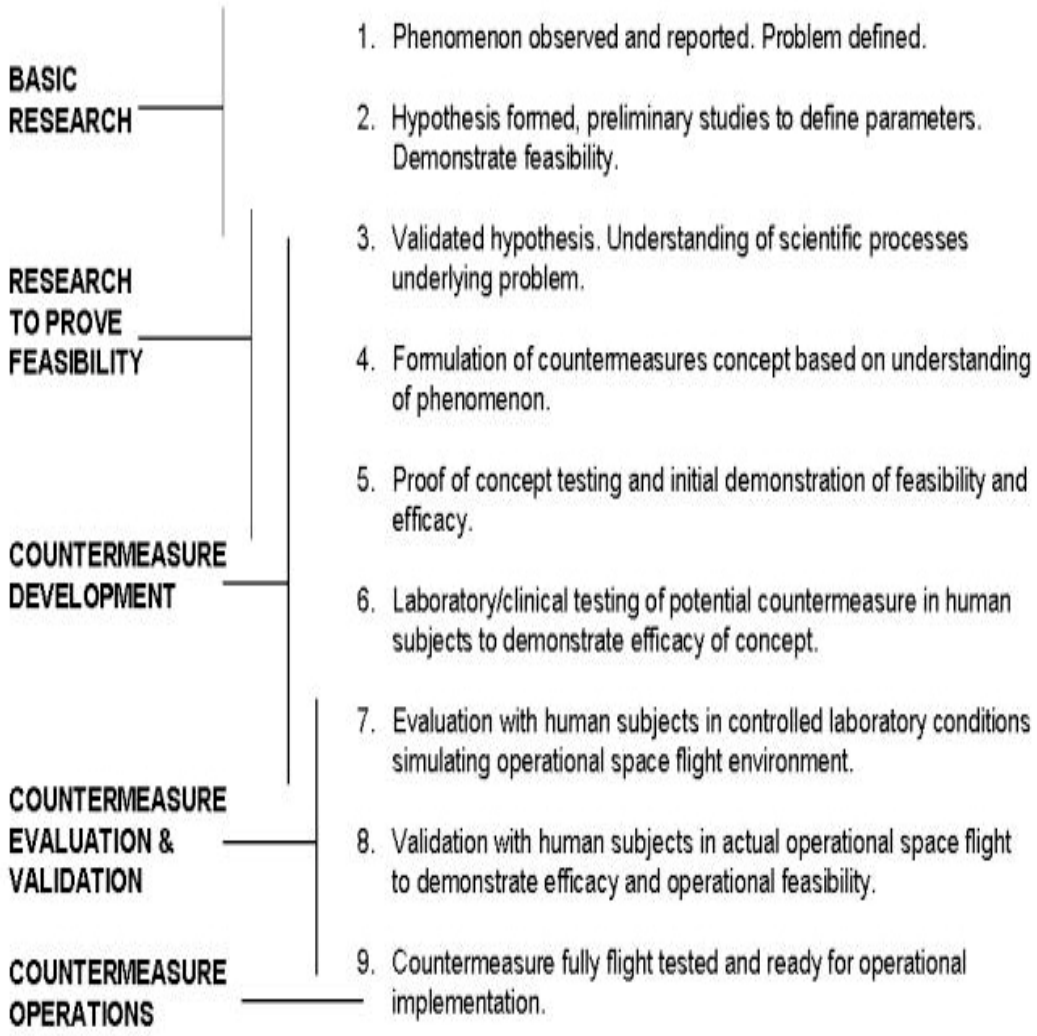
The current CPR is a product that has identified 55 risks and 250 critical questions. A more extensive overview as well as a list of all the risks and critical questions for the CPR should be reviewed by potential investigators on the Web site http://criticalpath.jsc.nasa.gov/.

III. Countermeasure Readiness Levels (CRL)

NASA's Biomedical Research and Countermeasures (BR&C) Program has developed a scale to allow NASA to define, assess, and quantify the level of "countermeasure readiness." The use of this scale allows NASA to determine how each funded research project fits into the countermeasure development "flow" and to monitor progress in countermeasure development. This section describes this scale and how it is used. **Each investigator must examine and understand the CRL scale and specify in the proposal the CRL that will result from the funding and conduct of their proposed research.** Figure 1 illustrates the CRL scale, which

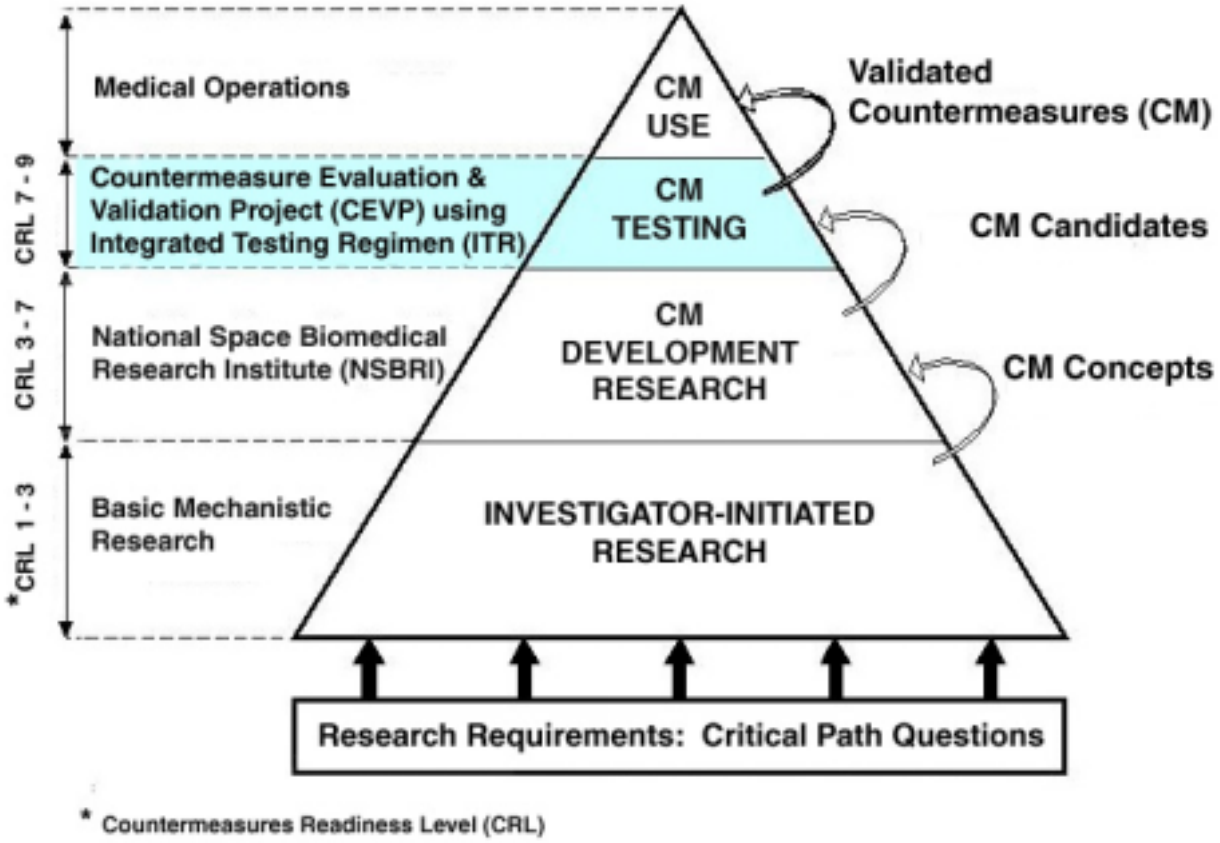
describes the level of scientific maturity of BR&C research from the fundamental studies that suggest potential countermeasures to studies that allow the systematic evaluation and validation of countermeasures ready for operational implementation.

Figure 1. Countermeasure Readiness Levels



Countermeasure development usually progresses through systematic research. Research flows through various levels of countermeasure readiness. Figure 2 represents this general progression. The boundaries between the types of activities are approximate. The CEVP is focused on CRL levels of 7 and 8 only. CEVP research will systematically evaluate and validate potential countermeasures that have completed laboratory testing, bridging the gap between research and space flight operations. A potential countermeasure ready for validation in flight is one that has a thorough, successful history of ground-based, clinical and/or flight analog testing.

Figure 2. Countermeasure Development Process



IV. Review and Selection Process

This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E. All proposals must comply with the general requirements of the Announcement as described in both Appendices A and E. Appendices B-D contain specific requirements and explanations for each opportunity above and beyond NASA-specified requirements. Appendix E outlines the NASA-

specified requirements for proposal submission and should be used for clarification and reference. Upon receipt, proposals will be reviewed for compliance with the requirements of this Announcement. This includes

1. Submission of complete proposals specified in this Announcement. Proposals must be responsive to the areas of program element emphasis described in this Announcement and include a project description that is not more than 20 pages in length.
2. Submission, as specified in the detailed instructions to investigators, of appropriate Institutional Review Board (IRB) or Animal Care and Use Committee (ACUC) certification for all proposals using human or animal test subjects.
3. Submission of a budget within the guidelines specified in this Announcement and for a funding period not exceeding three years in duration.
4. Proposals that are revised versions of proposals previously submitted to NASA must be clearly designated as such on the proposal cover page, and must contain an explanation of how the revised proposal has addressed criticisms from previous NASA review. This explanation should be presented in a separate section of **no more that two pages at the beginning of the project description**, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description.
5. Submission of all other appropriate forms as required by this NASA Research Announcement (refer to appropriate Appendix).

Note: Non-compliant proposals may be withdrawn from the review process and returned to the investigator without further review.

Compliant proposals submitted in response to this Announcement will undergo an intrinsic scientific or technical merit review. Only those proposals most highly rated in the merit review process will undergo the additional reviews for program relevance and cost.

Scientific or Technical Merit Review

A merit review of proposals submitted to this NRA will be conducted by panels of scientific or technical experts. A single set of discipline-specific panels, administered by NASA Peer Review Services, will evaluate all proposals submitted to this NRA. The number and diversity of experts required will be determined by the response to this NRA, and by the variety of disciplines represented in the proposals relevant to the research emphases described in Section I of this Appendix. Merit review panels will ***score proposals from 0-100***.

The score assigned by each panel ***will not be affected by the proposed cost of the work nor will it reflect the programmatic relevance of the proposed work to NASA***. However, the panels will be encouraged to include comments concerning the proposal's budget and relevance to NASA in the critique of each proposal, after it has been scored.

All of the following will be used in determining the merit score:

- **Significance:** Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or technology be advanced? What will be the effect of these studies on the concepts, methods, or products that drive this field? What is the likelihood that the proposed research will lead to new countermeasures or tests of the utility of countermeasures? Is there a significant societal or economic impact?

- **Approach:** Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Is the proposed approach likely to yield the desired results? Does the applicant acknowledge potential problem areas and consider alternative tactics? Are there strong interdisciplinary components?

- **Innovation:** Does the project employ novel concepts, approaches, or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

- **Investigator:** Are the scientists in the project, including collaborators, suitably trained for the proposed work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? Is the evidence of the investigator's productivity satisfactory?

- **Environment:** Does the scientific environment in which the work will be performed contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

Evaluation of Programmatic Relevance and Cost

A **second review** will evaluate the programmatic relevance and cost of all proposed work. Evaluation of the cost of a proposed effort includes consideration of the realism and reasonableness of the proposed cost and the relationship of the proposed cost to available funds. Is the proposal responsive to the needs of NASA or the NSBRI, ***as expressed in this NRA***? Programmatic relevance will include an evaluation of how the proposed work may help achieve an appropriate balance of scientific and technical tasks required by critical research issues faced. Evaluation of programmatic relevance will vary according to the specific element of this NRA. For example, CEVP proposals will be evaluated for operational relevance and feasibility of implementation.

Development of a Selection Recommendation

A selection recommendation will be developed based on the results of the two levels of review described above. The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. The development of selection recommendations is the responsibility of NASA for the individual proposals submitted to the Biomedical Research and Countermeasures (BR&C) Program and Advanced Human Support Technologies (AHST)

elements of this NRA and for CEVP proposals. The development of selection recommendations is the responsibility of the NSBRI for proposals submitted to the NSBRI elements of this NRA. Selections for funding of individual BR&C, AHST and CEVP proposals will be made by the Director of the Bioastronautics Research Division, Office of Biological and Physical Research (OBPR), and selection of NSBRI proposals will be made by the NSBRI management with the approval of the NSBRI Board of Directors. Final selection will be coordinated between the Bioastronautics Research Division at NASA Headquarters and the NSBRI to ensure programmatic balance and elimination of duplicate efforts.

NASA and the NSBRI reserve the right to select and make an award covering only a portion of an investigator's investigation, in which case the investigator will be given the opportunity to accept or decline such partial acceptance. In cases in which two or more proposals address similar problems and/or adopt similar approaches, NASA or the NSBRI may desire joint participation on the part of two or more investigators in a single project. Any negotiations prior to final decisions will occur only after the peer review of proposals has been completed. The selection review may also recommend changes in which program should fund a specific proposal (e.g., a proposal not selected for participation in an existing NSBRI team may be recommended for selection by the Bioastronautics Research Division or an individual proposal not selected as an individual proposal and not from a current NSBRI principal investigator may be recommended as an NSBRI team proposal.) In either case, acceptance of such a recommendation shall be at the discretion of the Principal Investigator. If a proposal submitted to OBPR is found to be more appropriate to satisfy the NSBRI requirements, the Principal Investigator will be expected to become a full member of the appropriate NSBRI team.

V. Program Reporting

It is expected that results from funded research will be submitted to peer-reviewed journals as the work is completed. Published papers must acknowledge NASA or NSBRI support. In addition, investigators whose proposals are selected must also provide annual reports on progress in achieving the goals of the research project.

Final Report. A final report is required that shall include a summary of completed research and a record of all scientific communications and peer-reviewed publications to date. This report must be submitted to the NASA Technical Monitor or to the NSBRI within 60 days after the end of the grant period.

VI. Support of Education and Outreach

NASA envisions that the selected proposals will be structured and operated in a manner that supports the country's educational initiatives and goals (including historically black colleges and universities and other minority universities), and in particular the need to promote scientific and technical education at all levels. NASA envisions that the selected proposals will support the goals for public awareness and outreach to the general public (see Appendix B). The selected investigators are invited to participate in NASA-funded educational programs.

OBPR Policy for Education (K-12) and Public Outreach

The proposal represents an opportunity for NASA to enhance and broaden the public's understanding and appreciation of the value of Biomedical Research and Countermeasures in the context of NASA's mission. Therefore, all investigators are strongly encouraged to promote general scientific literacy and public understanding of Biomedical Research and Countermeasures research through formal and/or informal education opportunities. If appropriate, proposals should include a clear and concise description of the education and outreach activities proposed. Examples include such items as involvement of students in the research activities, technology transfer plans, public information programs that will inform the general public of the benefits being gained from the research, and/or plans for incorporation of scientific results obtained into educational curricula consistent with educational standards.

Where appropriate, the supported institution will be required to produce, in collaboration with NASA, a plan for communicating to the public the value and importance of their work.

VII. Bibliography

1. **Life Sciences Program Tasks and Bibliography (Task Books)** for FY1995-2000 are available at http://peer1.nasaprs.com/peer_review/taskbook/taskbook.html/

2. **NSBRI Program Overview.** This document is available at http://www.nsbri.org/

3. **Space Life Sciences Ground Facilities Information Package.** This document is available at http://research.hq.nasa.gov/code_u/nra/current/NRA-01-OBPR-07/index.html

4. Information about space life sciences research publications can be found by using the National Library of Medicine's PubMed, LOCATORplus, and Gateway search systems. Coverage of space life sciences references in these systems has been enhanced by the SPACELINE Project through the support of NASA's Office of Biological and Physical Research. In addition, a space "limit" has been added to PubMed that permits limiting searches to a subset of space life sciences-related references only. Additional information may be obtained from the SPACELINE Project (phone: 301-295-2482; email: spaceline@usuhs.mil).
SPACELINE Project web address: http://spaceline.usuhs.mil
National Library of Medicine web address: http://www.nlm.nih.gov

5. **The Space Life Sciences Data Archive (LSDA)** is an online database containing descriptions and results of completed NASA-sponsored flight experiments. Descriptions are included of experiments, missions, procedures, hardware, biospecimens collected, personnel, and documents. Biospecimens that are available for research purposes are described in detail. A limited number of experiments contain final reports and spreadsheet data suitable for downloading. Data from human subjects are unavailable online for reasons of privacy.
Internet address: http://lsda.jsc.nasa.gov/
LSDA Help Desk: (281) 483-7876

Email: lsda@semail.jsc.nasa.gov

6. **Center for Advanced Studies in the Space Life Sciences** contains a list of workshops and seminars sponsored by the Center. The proceedings and final reports of these workshops are also posted as they become available at http://www.mbl.edu/CASSLS/

7. **Medical Policies and Requirements Document**. National Aeronautics and Space Administration, Medical Policy Board. Richard Williams, M.D., Chairperson. NASA Headquarters. This document is available at http://peer1.nasaprs.com/peer_review/prog/mpbhand.pdf

8. **A Strategy for Research in Space Biology and Medicine in the New Century.** National Academy of Science. National Research Council Committee on Space Biology and Medicine. Mary J. Osborn, Committee Chairperson. 1998. Washington DC: National Academy Press. http://www.nas.edu/ssb/csbm1.html/

9. **The NASA Strategic Program Plan for Space Radiation Research**. http://spaceresearch.nasa.gov/programs/1998_radiation_strat_plan.pdf/

10. **Space Physiology and Medicine, 3rd ed**. A. Nicogossian, C. Huntoon, and S. Pool. (Eds.). 1994. Philadelphia, PA: Lea & Febiger.

11. **Cell & Molecular Biology Research in Space**. *The FASEB Journal*, Vol. 13, Supplement, 1999.

12. **Radiation Protection Guidance for Activities in Low-Earth Orbit.** December 31, 2000. NCRP Report 132. Bethesda, MD: National Council on Radiation Protection and Measurements.

13. **Workshop on Space Flight Validation of Radiation Risk**. January 24-26, 1996. Universities Space Research Association, 3600 Bay Area Boulevard, Houston, TX, 77058.

14. **Shielding Strategies for Human Space Exploration**. J. W. Wilson, J. Miller, A. Konradi and F. A. Cucinotta, Editors. NASA CP-3360, December 1997, pp. 456. Also available from the NASA Langley Technical Reports Server, http://techreports.larc.nasa.gov/ltrs/ltrs.html/

15. **Acceptability of Risk >From Radiation - Application to Human Space Flight**. April 30, 1997. Symposium Proceedings No. 3. Bethesda, MD: National Council on Radiation Protection and Measurements.

16. **Modeling Human Risk: Cell & Molecular Biology in Context**. June 1997. Ernest Orlando Lawrence Berkeley National Laboratory Report, LBNL-40278. Berkeley, CA.

17. **Radiation Hazards to Crews of Interplanetary Missions: Biological Issues and Research Strategies**. 1996. Washington, DC. Task Group on the Biological Effects of Space

Radiation. Space Studies Board Commission on Physical Sciences, Mathematics and Applications, National Research Council. National Academy Press.

18. **Task Force on Countermeasures.** This report incorporates the output of the Countermeasures Task Force, the Vestibular Countermeasures Task Group, and the Behavior and Performance Working Group into a unified document. This document is available at http://peer1.nasaprs.com/peer_review/prog/countermeasures/countermeasures.html/

19. **International Workshop on Cardiovascular Research in Space**. *Medicine and Science in Sports and Exercise*, Volume 28, Number 10 Supplement, 1996.

20. **Muscle Research in Space: International Workshop**. *International Journal of Sports Medicine*, Volume 18, Supplement 4, S257-S331, 1997.

21. **Space Neuroscience Research**. *Brain Research Reviews*, Volume 28, Numbers 1/2, Special Issue, 1998.

22. **International Workshop on Bone Research in Space**. *Bone, Official Journal of the International Bone and Mineral Society*, Volume 22, Number 5 (Supplement), 1999.

23. **Space Human Factors Project Plan (2000) and the Space Human Factors Project Implementation Plan, FY00-FY01 (2000).**
http://peer1.nasaprs.com/peer_review/prog/prog.html

24. **Small Clinical Trials: Issues and Challenges.** Institute of Medicine, National Academy Press, Washington, DC. http://www.nap.edu/books/0309073332/html/

25. **Sex and Gender: Exploring the Biological Contributions to Human Health**. *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508 (1994).*

Multiple Opportunities for Ground-Based Research in Space Life Sciences Technical Description

Opportunity to Submit Individual Investigations for the Biomedical Research and Countermeasures or Advanced Human Support Technology Programs

NOTE: This appendix should only be used for scientists interested in conducting an individual, independent research project.

I. Introduction

The Biomedical Research and Countermeasures (BR&C) Program directly supports NASA's missions in the Office of Biological and Physical Research and the Human Exploration and Development of Space Enterprises. It also responds directly to the requirements, approved by the Office of the Chief Health and Medical Officer, which deal with the health and safety of human space travel (see *Medical Policies and Requirements Document*, Bibliographic Reference #7 of Appendix A).

The goals of this program are to

- develop an understanding of the physiological mechanisms that are responsible for space flight-related biomedical and behavioral changes in humans in support of countermeasure development;
- develop countermeasures that allow humans to live and work in microgravity for long durations, minimize the risks in readapting to gravity, and optimize crew safety, well-being, and performance; and
- identify, characterize, and mitigate (preventing and reducing) health, environmental, and other operational human medical risks associated with space exploration.

II. Biomedical Research and Countermeasures (BR&C) Program Emphases

Elements and Emphases for FY 2002

The emphasis of the current ground-based component of this program is to develop insights into physiologic changes that are likely to occur as a consequence of extended periods of flight. The BR&C Program supports basic, applied and clinical research. Researchers may use hypogravity

simulation models (e.g., bed rest, unilateral lower limb suspension, tail suspension, etc.) or hypergravity produced by centrifugation for their research studies. Experiments may use human subjects, animal models, or other appropriate models in the development of countermeasures. The program is composed of five research elements, each focused on the development and ultimate use of countermeasures to the deleterious effects of space flight: 1) Physiology, 2) Behavior and Performance, 3) Environmental Health, 4) Clinical Research in Support of Space Missions, and 5) Radiation Health.

Mechanistic research is solicited that supports the development of ground-based biomedical countermeasures to the effects of space flight. A countermeasure to help astronauts is any means or procedural strategy that prevents or reduces the negative effects of space or aids in the recovery upon return to Earth. It should be noted that the astronaut corps is diverse, comprised of men and women 30-60 years of age and of various ethnic backgrounds. Countermeasures should be robust enough to be efficacious across this population and be tailored for individual specificity. **This program encourages integrated approaches that study interactions that occur between different physiological systems in the design and application of potential countermeasures.** Identifying the effects of experimental interventions on non-target systems as well as the targeted system is deemed to be of particular importance. Research is also sought to support the solution to operational and clinical problems. This section describes the elements and research emphases within the BR&C Program. **High priority in FY 2002 will be given in particular to proposals for research in the areas of Radiation Health and Clinical Studies.**

It is expected that the average total annual (direct+indirect) cost of selected proposals will be between $200,000 and $250,000. In general, the total annual cost of a single proposal may not exceed $400,000.

1. Physiology

Proposals are requested for ground-based studies that will lead to a better understanding of the effects of space flight and exposure to microgravity on physiological function. Space physiology has included 1) fluid volume and cardiopulmonary, including cardiovascular alterations; 2) musculoskeletal, including bone loss and muscle alterations and atrophy; 3) neuroscience, including vestibular function, circadian rhythms, sensorimotor function, and endocrine control; 4) immunology, infection, and hematology; 5) food, nutrition, and metabolism, and 6) integrative physiology; as well as 7) advanced technology development within the above elements. Research proposals in other areas of physiology are also solicited (e.g., renal, endocrine physiology, etc.). Studies that use integrated approaches are particularly encouraged. Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov.

Contact: Bruce Hather, Ph.D./Bioastronautics Research Division
Telephone: 202-358-1796
Email: bhather@hq.nasa.gov

2. Behavior and Performance

The Behavior and Performance element of the program addresses issues of 1) perception and cognition, 2) human physical performance, 3) personal, interpersonal, and group dynamics (coping, response to stress, etc.); 4) habitability, and 5) sleep and circadian rhythms. Physiological studies should be directed toward understanding the effects of responses to space flight on behavior and performance measures.

This element supports experiments designed to understand the mechanisms by which microgravity, confinement, cumulative sleep loss, mission design and events, spacecraft environment, and noise and light affect the behavior and performance of flight crews and ground-support crews. It also addresses psychosocial, gender, and cross-cultural aspects of human missions in space. Studies of relationships between individuals and individuals in groups are also addressed. Existing databases and ground simulations in extreme and isolated analogs and test beds may be used to extrapolate to responses that might be expected in long-duration space flight. Behavior and performance research priorities for ground-based studies include

a. Psychological Research

Research is solicited on: the development and validation of predictive tools for the assessment of psychological well-being, cognitive processing, mood, and emotion; especially as those are affected by multicultural and gender variables in long-duration space missions.

b. Psychiatric Issues

Research is required to detect and treat behavioral disorders that might occur in locations remote from usual health care facilities, e.g., during long-duration space flight.

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov. For a broad, detailed listing of NASA Life Sciences Behavior and Performance research priorities, the Countermeasures Task Force Report on Behavior and Performance can be obtained online at
http://research.hq.nasa.gov/code_u/code_u.cfm

Contact: David L. Tomko, Ph.D./Bioastronautics Research Division
Telephone: 2 02-358-2211
Email: dtomko@hq.nasa.gov

3. Environmental Health Research

Research within the Environmental Health element includes three interrelated disciplines, each dealing with a specific aspect of the spacecraft environment – Barophysiology, Microbiology, and Toxicology. The Environmental Health element has established the following goals: (1) to understand the effects of the spacecraft environments on humans and other organisms; and (2) to develop standards and countermeasures, where necessary, to optimize crew health, safety, and productivity.

For FY 2002, proposals are particularly sought for ground studies to determine the effects of potential toxins found on the International Space Station on human health. Since the work and living environment of the space flight crew is one and the same, the individual may be exposed to these potential toxins for extended times as compared to limited work hours here on Earth. Additionally, proposed studies that evaluate the added risk of several potential toxins with space radiation are encouraged. Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at: http://criticalpath.jsc.nasa.gov.

Contact: Bette Siegel, Ph.D./Bioastronautics Research Division
Telephone: 202-358-2245
Email: bsiegel@hq.nasa.gov

4. Clinical Research in Support of Space Missions (Medicine in Extreme Environments)

The Clinical Research in Support of Space Missions element of the program will focus on the development of medical knowledge and technologies required to maintain human health and performance in space and on return to Earth. Medical knowledge must be expanded so that the practice of Space Medicine in the microgravity environment can be evidence based. Medical and surgical procedures and treatment and imaging systems are required to diagnose and treat illnesses and injuries that may occur in space. The Clinical Research in Support of Space Missions element of the program will support research required to improve, or answer specific questions about in-flight diagnosis, therapy, and postflight rehabilitation.

a. Diagnosis

Ground-based research analogs for space flight research are required to complete the understanding of the patho-physiology, diagnosis and therapeutic modalities required for implementation of an evidence-based practice of Space Medicine. Proposals for the development of non-invasive diagnostic tests and autonomous and semi-autonomous patient monitoring systems are requested. Research is also sought for the development of medical information systems that support the onboard medical provider.

b. Therapy

High priority will be given to research proposals to study the mechanisms of changes that could occur during space flight in the therapeutic effectiveness and adverse drug interactions of medications for common illnesses. Proposals are sought for research to enhance surgical capabilities in space. High priority will be given to proposals that investigate the application of fiber optic-based and minimally invasive surgical techniques.

Proposals are sought in medical education focused on the development and maintenance of medical capabilities for both physicians and non-physician crew medical officers. Priority will be given to those research proposals that develop and test new training paradigms. Proposals are a priority that address the development of space flight

treatment capabilities for acute medical and surgical emergencies such as wounds, lacerations, and burns; toxic exposures; decompression illness; dental, ophthalmologic, urologic, gastrointestinal, and gynecologic emergencies.

c. Rehabilitation

Proposals are sought for research to develop effective rehabilitation techniques for deconditioned space travelers on their return to Earth. Priority will be given to proposals addressing rehabilitation after long-duration space flight.

d. Pharmaceuticals and Blood Replacement Solutions

Proposals are sought for ground-based research to enhance the "shelf-life" and effectiveness of pharmaceuticals, intravenous fluids, and blood replacement substances, which are stored for extended periods of time and would be required for clinical care of patients in extreme environments (e.g., radiation resistant, storage at ambient temperature, small volume, etc.).

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at http://criticalpath.jsc.nasa.gov.

Contact: Victor S. Schneider, M.D./Bioastronautics Research Division
Telephone: 202-358-2204
Email: vschneider@hq.nasa.gov

5. Radiation Health

The Radiation Health element of the program supports research in the areas of 1) radiation physics, 2) biological effects of shielding materials, 3) genetic biological predisposition, and 4) bioengineering and radiation protection. For FY 2002, the primary area of emphasis for the Space Radiation Health element is the *reduction of radiation risk* based on development of mechanistic insights into the biological effects of radiation. Purely phenomenological approaches, e.g., testing of pharmacological substances with presumed radioprotective effects without developing new knowledge, are not acceptable. Instead, proposals are required to be hypothesis-driven and are expected to obtain their data in ground-based experimental radiobiology studies with proton and high-energy heavy ion beams in the energy range corresponding to space radiation.

Scientists working in rapidly developing areas of life sciences not necessarily associated with the study of radiation are particularly encouraged to consider the contributions that their field of study can make to Radiation Health, and to propose investigations relevant to the Space Radiation Health element. Proposals are required to provide evidence for expertise in radiation, either by reference to the Principal Investigator's work or by the inclusion of active collaborators expert in radiation research.

High-priority research proposals will

1. Determine carcinogenic risks following irradiation by protons and HZE particles.
2. Determine how cell killing, induction of chromosomal aberrations, or carcinogenesis vary as a function of the thickness and composition of radiation shielding.

3. Increase the confidence of extrapolation to humans from knowledge of radiation-induced genetic alterations or carcinogenesis in rodents.
4. Determine if exposure to heavy ions at levels occurring in deep space pose a risk to the integrity and function of the central nervous system.
5. Lead to significant advances in our understanding of cancer risk, consequences of CNS damage, and acute and early damage due to solar particle events.
6. Link biological mechanisms to significant improvements in accuracy of prediction of radiation risk for humans in space (especially carcinogenesis).

Additionally, studies are requested that lead to significant advances in our understanding of genetic mechanisms of radiation damage and repair in cells and tissues, especially those aspects that are complementary to research in genomic instability, which have been jointly funded with the National Cancer Institute. Proposals addressing genetic sensitivity to space radiation and genetic intervention to alter such sensitivity are encouraged. **Proposals are requested that test methods to protect from or counteract the effects of high energy radiation damage while increasing new knowledge regarding the mechanisms of organismal protection from radiation or in their recovery from radiation damage.**

Proposals are of interest that are based on basic mechanisms of molecular biology that are likely to result in development of biological countermeasures in humans that could lead to prevention or intervention (including genetic or pharmacological agents) against effects of radiation damage in space.

NASA has signed agreements with Loma Linda University Medical Center related to the use of proton beams and with Brookhaven National Laboratory (Brookhaven) for the use of heavy ion beams at the Alternating Gradient Synchrotron (further details are provided in Section 5.0 of *Space Life Sciences Ground Facilities Information Package*). A new facility at Brookhaven, the Booster Applications Facility (BAF), is under construction. It is expected to become operational in 2003 and will deliver beams of protons and heavy ions ranging up to gold, at energies between tens and thousands of MeV/nucleon. The BAF includes irradiation stations, beam controls and laboratory facilities required for most radiobiological investigations. **NASA negotiates beam delivery directly with these institutions, and investigators proposing to use these irradiation facilities should not include the cost of beam time in their budgets. However, investigators should include the cost of carrying out the experiments, including travel to these facilities.**

Experimental studies not directly using protons or heavy ions in the relevant energy range or not directly relevant to the interpretation of experiments already conducted with such radiation will not be funded. The Brookhaven BAF will become operational in 2003. Research proposals are encouraged that use the BAF to answer the focused questions above. Proposals should take into account the impact of gender, age, nutrition, stress, genetic predisposition, or sensitivity to other factors of importance in managing space radiation risks.

Proposals must represent questions and priorities enumerated in the Critical Path Roadmap at http://criticalpath.jsc.nasa.gov.

Contact: Walter Schimmerling, Ph.D./Bioastronautics Research Division
Telephone: 202-358-22005
Email: wschimm@hq.nasa.gov

III. Advanced Human Support Technology Program (Space Human Factors Engineering Element)

Emphases for FY 2002

The Space Human Factors Engineering (SHFE) element solicits research proposals in the areas of 1) habitability and work environment, 2) training, 3) mission support, 4) crew performance and workforce characteristics, 5) data analysis and design, and 6) workload and task characteristics. The investigator should highlight, where possible, how the results of the proposed research can be used (at the earliest possible time) to support operations on the ISS or in training in preparation for space flight. Proposals for research in other areas relevant to the SHFE element may be submitted in response to this NRA but will likely receive lower priority for funding.

The research focus for each of the areas of emphasis (not in priority order) follows:

Habitability and Work Environment

Methods for objectively or quantitatively measuring habitability features are needed. This NRA solicits studies to develop tools for predicting the effects of combinations of habitability-related issues (e.g., noise, visual environment, privacy) on crew performance and safety.

Training

This NRA solicits studies that focus on deciding when training is needed (i.e., just in time training), and how to determine if training prior to a planned or unplanned task is absolutely essential or just helpful. Proposals are sought that would study the effectiveness of embedded training in actual operational equipment; supporting analyses of risk/error and training benefit should be compared to traditional methods. Studies to assess team training, and strategies to measure learning both for the group and the individual, are also solicited.

Mission Support

Proposals to determine the appropriate composition of automated tasks overseen by the workforce (flight and ground support crews), and research to determine the effect of "online" documentation of procedures, are solicited. Proposals are also solicited to determine how best to communicate mission performance data to crews, involve crews during the planning of off-nominal situations or when new information requires changes in operations, and how to develop strategies and/or technologies which aid and measure the crews ability to functionally make these changes.

Crew Performance (and Workforce Characteristics)

Proposals are solicited that lead to technologies or processes that monitor human/machine performance (within adjustable limits) and allows appropriate and timely feedback to the monitoring crew for task replanning.

Data Analysis and Design

Proposals for improved methods and tools for data collection, analysis and organization are solicited. Typical challenges in this area include effective use of mission equipment and crew; efficient transmission, archiving, and distribution of data; and rapid access to mission data for real-time replanning. Proposed research should include human factors issues in design of human interfaces and in understanding of human use of scientific and engineering data.

Workload and Task Characteristics

Proposals for non-intrusive methods of workload assessment including the effects of levels of workload on performance are solicited. Proposals are also solicited for development of models that predict the effects of various schedules and workloads on human performance, with emphasis on measuring the effects of how task allocation between humans and automated systems affect both crew and system performance.

Further information on the SHFE element of the Advanced Human Support Technology Program (reference 23) can be found at http://peer1.nasaprs.com/peer_review/prog/prog.html

Additional information about the Advanced Human Support Technology Program is available from

Charles J. Barnes, Ph.D.
NASA Headquarters, Code UB
Washington, DC 20546
Telephone: 202-358-2365
Fax: 202-358-4168
Email: cbarnes@hq.nasa.gov

Contact: Mr. Thomas Rathjen/NASA Johnson Space Center
Telephone: 281-483-3651
Email: trathjen@ems.jsc.nasa.gov

IV. Application Procedures for Individual Investigators Proposing to the Biomedical Research and Countermeasures or Advanced Human Support Technology Program

Instructions for Notice of Intent and Proposal Submission

Proposals for individual investigator grants must comply with the general requirements of this research opportunity as described in this appendix (Appendix B). Appendix E outlines general NASA-specified requirements for proposal submission and should be used for clarification and reference. This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E.

SYS-EYFUS Registration for All Applicants

SYS-EYFUS is an electronic system used by NASA Headquarters to manage research solicitation activity, plan for the receipt of research proposals, track the receipt and peer evaluation of these proposals, and manage funded research (grants, cooperative agreements, etc.) sponsored by NASA's Office of Equal Opportunity (Code E), Office of Earth Science (Code Y), Office of Human Resources & Education Division (Code F), Office of Biological and Physical Research (Code U), Office of Space Science (Code S), and the Office of Space Flight (Code M). SYS-EYFUS also supports the funding and administration of awards pursuant to selection of these research opportunities.

All investigators planning to submit a proposal to this solicitation are requested to register online with SYS-EYFUS. Comprehensive help, instructions, and contact information are provided online. SYS-EYFUS can be accessed at the following address:

http://proposals.hq.nasa.gov/

If you have previously registered with SYS-EYFUS, you are requested to verify and update your user information. If you have forgotten your user ID or password, select the "Forgot Your Password" option and type in your first and last name to search our database. The system will send an automatic email message with your username and password to the email address listed in our database.

Instructions for Preparing a Notice of Intent

All investigators planning to submit a proposal in response to this solicitation are requested to submit a **non-binding** notice of intent (NOI) to propose by November 30, 2001, via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

Submission of a notice of intent is strongly encouraged, but not mandatory.

- Login to SYS-EYFUS and select "New Notice of Intent."
- The Division Specific Opportunities screen will appear. In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Notice of Intent submission Form. All fields are required.
  a. For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that

the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002.

- Click on "Submit NOI Page."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name, and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the NOI. After you are done, click on "Continue." IMPORTANT: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Members Page, your NOI will be displayed. Click on "Resubmit NOI Page" to complete your NOI submission.
- You may edit and resubmit your NOI at any time before the submission deadline of November 30, 2001. Once you submit an NOI, it cannot be deleted. For title, team member, or any other changes, please edit your existing NOI and resubmit changes to avoid duplicate records.

Instructions for the Preparation of Proposals

An original signed proposal, plus twenty (20) complete copies of the proposal, should be mailed to the address indicated and in the manner described of this document.

All proposals submitted to the Bioastronautics' Biomedical Research and Countermeasures Program must include the completed cover page form as described in this Appendix. The name of the Principal Investigator should appear in the upper right hand corner of each page of the proposal, except on the cover page form where special places are provided for this information. Note that the proposal must specify the period of performance for the work described; periods of performance may be for any duration up to three (3) years but should be suitable for the project proposed.

The proposal must include the following material, in this order:

(1) Proposal Cover Page: Solicited Proposal Application, including certification of compliance with U.S. code (if applicable). One signed original required.

Please see "How to Submit Proposal Cover Page Information" below for instructions on how to complete the proposal cover page information.

(2) Transmittal Letter or Prefatory Material, if any (see Appendix E for details)

(3) Proposal Title Page, with Notice on Restriction on Use and Disclosure of Proposal Information, if any (see Appendix E for details)

(4) Project Description. The length of the Project Description section of the proposal cannot exceed 20 pages using regular (12 point) type. Referenced figures must be included in the 20 pages of the Project Description. The Bibliography section is not considered part of the 20-page project description. Proposals that exceed the 20-page limit for the project description (22-page limit for revised proposals; see below) will not be reviewed. The proposal should contain sufficient detail to enable reviewers to make informed judgments about the overall merit of the proposed research and about the probability that the investigators will be able to accomplish their stated objectives with current resources and the resources requested. In addition, the proposal should clearly indicate the relationship between the proposed work and the research emphases defined in this Announcement. Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

New applications, where the investigator has received NASA funding in related fields from 1999 through 2001, must present results and evidence of progress of the associated NASA-supported research as part of the project description.

Revised applications (revisions of 1999, 2000, or 2001 submissions) must be so designated on the proposal cover page and explained in the project description. This explanation should be presented in a separate section of **no more than two pages** at the beginning of the project description, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description. Changes within the proposal may be highlighted by appropriate bracketing, indenting, or changing of typography. Clearly present any work done since the prior version was submitted. **Revised applications that do not address the criticisms in the previous review will be considered nonresponsive and will be returned without review.**

(5) Management Approach

Each proposal must specify a single Principal Investigator who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. In proposals that designate several senior professionals as key participants in the research project, the management approach section should define the roles and responsibilities of each participant and note the proportion of each individual's time to be devoted to the proposed research activity. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation.

(6) Personnel/Biographical Sketches

The biographical sketch for each investigator should not exceed two pages. If the list of qualifications and publications exceeds two pages, select the most pertinent information (see Appendix E for details).

(7) Other Support (see Appendix E for details)

(8) Facilities and Equipment (see Appendix E for details)

(9) Special Matters (specific information on animal or human subjects protocol approval required, if applicable)

The Special Matters section must contain a statement from the investigator's institution that states that the proposed work will meet all Federal and local human subject requirements and animal care and use requirements, if applicable. Note that no animal subjects may be utilized unless specific information justifying and describing their use is included in the proposal. Policies regarding the protection of human research subjects in NASA-sponsored research are detailed in NASA Management Instruction (NMI) 7100.8B (Protection of Human Research Subjects), and animal care and use requirements are detailed in the NASA Code of Federal Regulations (CFR) 1232 (Care and Use of Animals in the Conduct of NASA Activities), both of which are available from the Office of Biological and Physical Research, Code UB, NASA Headquarters, Washington, DC, 20546. Assurance of compliance with human subject or animal care provisions is required on Form A, to be submitted with each proposal. In addition, a letter signed by the chairperson of the Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC), or both, as appropriate, regarding approval of the experimental protocol, should be included with each copy of the proposal. If IRB or IACUC review is unavoidably delayed beyond the submission of the application, enter "Pending" on Line 9b or 10a of Form A, and be advised that the certification must be received within 60 days after the due date for which the application is submitted. If certification is not received within 60 days after the application due date, the application will be considered incomplete and will not be reviewed. NASA shall require current IRB or IACUC certification prior to each year's award. All U.S., non-NASA proposals providing IACUC approval must also contain the institution's Public Health Assurance number.

(10) Detailed Budget

NASA is expected to be operating on the basis of full cost accounting as soon as possible, including all Civil Service salaries with overhead. In the interim period, proposals should use the accounting method authorized at their institutions at the time proposals are due and for the entire proposed period of performance. Funds to support the Resident Research Assistant (RRA) Postdoctoral Program costs (e.g., stipend, travel, computer time, supplies, etc.) are to be budgeted within the NASA intramural Principal Investigator budget.

The budget must include travel funds for the Principal Investigator to attend a biannual BR&C Principal Investigator meeting. If other travel is planned, the proposal budget should include appropriate travel funds for visits to NASA field centers (as appropriate) and presentation of findings at professional society meetings.

(11) Supporting Budgetary Information

In this solicitation, the terms "cost" and "budget" are used synonymously. Sufficient proposal cost detail and supporting information are required; funding amounts proposed with no explanation (e.g., Equipment: $1,000, or Labor: $6,000) may cause delays in evaluation and award. Generally, costs will be evaluated for realism, reasonableness, allowability, and allocation. The budgetary forms define the desired detail, but each category should be explained

in this section. Offerors should exercise prudent judgment in determining what to include in the proposal, as the amount of detail necessarily varies with the complexity of the proposal.

The following examples indicate the suggested method of preparing a cost breakdown:

Direct Labor
Labor costs should be segregated by titles or disciplines with estimated hours and rates for each. Estimates should include a basis of estimate, such as currently paid rates or outstanding offers to prospective employees. This format allows the Government to assess cost reasonableness by various means including comparison to similar skills at other organizations.

Other Direct Costs
Please detail, explain, and substantiate other significant cost categories as described below:
Subcontracts: Describe the work to be contracted, estimated amount, recipient (if known), and the reason for subcontracting.
Consultants: Identify consultants to be used, why they are necessary, the time they will spend on the project, and the rates of pay (not to exceed the equivalent of the daily rate for Level IV of the Executive Schedule, exclusive of expenses and indirect costs).
Equipment: List separately. Explain the need for items costing more than $5,000. Describe basis for estimated cost. General purpose equipment is not allowable as a direct cost unless specifically approved by the NASA Grant Officer. Any equipment purchase requested as a direct charge must include the equipment description, how it will be used in the conduct of the basic research proposed, and why it cannot be purchased with indirect funds.
Supplies: Provide general categories of needed supplies, the method of acquisition, and estimated cost.
Travel: Describe the purpose of the proposed travel in relation to the grant and provide the basis of estimate, including information on destination and number of travelers where known.
Other: Enter the total of direct costs not covered previously. Attach an itemized list explaining the need for each item and the basis for the estimate.

Indirect Costs
Indirect costs should be explained to an extent that will allow the Government to understand the basis for the estimate. Examples of prior year historical rates, current variances from those rates, or an explanation of other basis of estimates should be included. Where costs are based on allocation percentages or dollar rates, an explanation of rate and application base relationships should be given. For example, the base to which the General and Administrative (G&A) rate is applied could be explained as application base equals total costs before G&A less subcontracts.

All awards made as a result of this NRA will be funded as grants. However, while proposals submitted by "for profit" organizations are allowed, they cannot include a "fee."

(12) Appendices, if any (reviewers are not required to consider information presented in appendices)

How to Submit Proposal Cover Page Information

All investigators planning to submit a proposal in response to this solicitation must electronically submit proposal cover page information online and provide a hard copy of the cover page attached to each proposal copy by January 31, 2002. The proposal cover page can be submitted and printed via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS.
- To submit a New Proposal Cover Page, click the "New Proposal Cover Page" option from the SYS-EYFUS Options screen, and the New Proposals Cover Page screen will appear.
- If you previously submitted an NOI in response to this solicitation, choose to carry over the existing NOI. This option will populate the cover page fields with the NOI information. Edit the information as necessary, click "Continue" and proceed to the instructions for the Proposal Cover Sheet Submission Form below.
- If you did not previously submit an NOI, click on New Proposal Cover Page option, and the Division Specific Opportunities screen will appear.
- In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Proposal Cover Page Submission Form. Fill in all the fields. All fields are required.
  For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002. Click on "Continue."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the proposal. After you are done, click on "Continue." **IMPORTANT**: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Member Page, the Proposal Options Page appears.
- Please fill out the budget form by clicking on the "Budget" button, filling in project costs, and clicking "Continue." This will bring you to the Proposal Budget Review Page. Click "Continue" if the information is correct.
- After verifying your budget information, you will be returned to the Proposal Options Page. Click the "Show/Print" button.
- At the page entitled Proposal Information Item List click "Continue" to preview your Proposal Cover Page. Print the cover page from your Internet browser once you have reviewed the information. The cover page must be signed by both the Principal Investigator

and the authorizing official and attached to the font of your proposal before submission of hard copies to NASA.

- You may edit and resubmit your proposal cover page at any time before the submission deadline of January 31, 2002. Please note that once you submit a proposal cover page, it cannot be deleted. For title, team member, budget or any other changes, please edit your existing proposal cover page and resubmit changes to avoid duplicate records.
- One (1) signed original and twenty (20) copies of the proposal must be received by 5:00 PM on January 31, 2002, at the following address:

  NASA Peer Review Services
  Subject: 01-OBPR-07
  500 E Street SW, Suite 200
  Washington, DC 20024

V. Review and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the Review and Selection Process.

VI. Eligibility

All categories of U.S. institutions are eligible to submit proposals in response to this NRA. Principal Investigators may collaborate with universities, Federal Government laboratories, the private sector, and state and local government laboratories. In all such arrangements, the applying entity is expected to be responsible for administering the project according to the management approach presented in the proposal.

The applying entity must have in place a documented base of ongoing high quality research in science and technology or in those areas of science and engineering clearly relevant to the specific programmatic objectives and research emphases indicated in this NRA. Present or prior support by NASA of research or training in any institution or for any investigator is not a prerequisite to submission of a proposal or a competing factor in the selection process.

All types of institutions are eligible to submit proposals in response to this NRA, but only the U.S. investigators and U.S. institutions that collaborate in a selected proposal qualify for funding of their portion of any collaborative research. Proposals without substantive collaboration from a U.S. entity will not be reviewed except in the case of CEVP proposals submitted by investigators from the International Life Sciences Working Group Space Agencies members. CEVP proposals approved for funding by the international member states will be reviewed.

VII. Foreign Proposals

Only ground-based proposals submitted in response to this NRA from U.S. entities, or from non-U.S. entities that involve substantive co-investigator collaboration from a U.S. entity, will be

reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Proposals from non-U.S. entities with significant co-investigator collaboration from a U.S. entity, must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

All proposals from non-U.S. entities which involve substantive co-investigator collaboration from a U.S. entity must be typewritten in English and comply with all other submission requirements stated in this NRA. These proposals will undergo the same evaluation and selection process as those originating in the U.S. All proposals must be received before the established closing date. Sponsoring foreign government agencies or funding institutions for proposals from non-U.S. entities meeting the above guidelines may, in exceptional situations, forward a proposal without endorsement to the above address if endorsement is not possible before the announced closing date. In such cases, the NASA sponsoring office should be advised when a decision on endorsement can be expected.

Successful and unsuccessful non-U.S. investigators will be contacted directly by the NASA sponsoring office. Copies of these letters will be sent to the sponsoring government agency or funding institution. Should a non-U.S. proposal with significant U.S. participation be selected, NASA's Office of External Relations will arrange with the foreign sponsoring agency or funding institution for the proposed participation on a non-exchange-of-funds basis, in which NASA and the non-U.S. sponsoring agency or funding institution will each bear the cost of discharging their respective responsibilities.

Depending on the nature and extent of the proposed cooperation, this arrangement may entail

1. a letter of notification by NASA;
2. an exchange of letters between NASA and the sponsoring foreign governmental agency; or
3. a formal Agency-to-Agency Memorandum of Understanding (MOU).

Export Control Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

Proposals including foreign participation must include a section discussing compliance with U.S. export laws and regulations, e.g., 22 CFR Parts 120-130 and 15 CFR Parts 730-774, as applicable to the circumstances surrounding the particular foreign participation. The discussion must describe in detail the proposed foreign participation and is to include, but not be limited to, whether or not the foreign participation may require the prospective investigator to obtain the prior approval of the Department of State or the Department of Commerce via a technical assistance agreement or an export license, or whether a license exemption/exception may apply. If prior approvals via licenses are necessary, discuss whether the license has been applied for or

if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available at http://www.pmdtc.org and http://www.bxa.doc.gov. Investigators are advised that under U.S. law and regulations, spacecraft and their specifically designed, modified, or configured systems, components, and parts are generally considered "Defense Articles" on the United States Munitions List and subject to the provisions of the International Traffic in Arms Regulations (ITAR), 22 CFR Parts 120-130.

APPENDIX C
NRA 01-OBPR-07

Multiple Opportunities for Ground-Based Research in Space Life Sciences Technical Description

Opportunity to Participate on a National Space Biomedical Research Institute Team

NOTE: Only investigators who are applying to join one of the pre-existing NSBRI research teams should use this appendix for the preparation of their application.

I. Introduction

The National Space Biomedical Research Institute (NSBRI), a private, non-profit organization, invites research proposal applications to join an existing ground-based research team in one of the twelve active research areas:

1. *Bone Loss* – Addressing bone loss and weakening during space flight with the inherent fracture risks
2. *Cardiovascular Alterations* – Addressing the inflight occurrence of cardiac dysrhythmia and postflight impairment of the cardiovascular response to orthostatic and exercise stress
3. *Human Performance Factors, Sleep and Chronobiology* – Investigating maintenance of high cognitive performance and vigilance despite environmental stress and sleep disturbances
4. *Immunology, Infection and Hematology* – Addressing immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia
5. *Integrated Human Function* – Developing an overall understanding of the human body's response to space flight
6. *Muscle Alterations and Atrophy* – Focusing on the loss of skeletal muscle mass, strength, and endurance that accompanies space flight
7. *Neurobehavioral and Psychosocial Factors* – Investigating methods and tools that can be utilized to enable crews to cope with stress, isolation and compatibility
8. *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders
9. *Nutrition, Physical Fitness and Rehabilitation* – Developing methods to maintain health and fitness before, during, and after space flights
10. *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment;
11. *Smart Medical Systems* – Developing new methods of medical monitoring, diagnosis, and therapy for use on space missions
12. *Technology Development* – Developing instrumentation and other technological products that will enhance the research of the other teams and benefit people on Earth.

Each of the twelve research teams consists of a set of individual, coordinated, and complementary projects focused on a common theme. Team management and coordination is

the responsibility of a program director called a **Team Leader**. The current Team Leaders for these twelve teams are listed in Section III of this Appendix.

Applications will be accepted from all categories of organizations, public and private, and for-profit and non-profit, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. The mechanism of support shall be an NSBRI subagreement with funds provided by the National Aeronautics and Space Administration (NASA) through a cooperative agreement (Cooperative Agreement NCC 9-58 with NASA's Lyndon B. Johnson Space Center). Annual renewal awards are subject to an independent, external review. Potential foreign applicants should note that, normally, the country of origin, not the NSBRI, must fund applications from non-U.S. organizations. Potential foreign applicants should coordinate their application with both the NSBRI and the appropriate funding agency in their own country.

II. Background

The NSBRI is responsible for the development of countermeasures against the deleterious effects of long-duration space flight and applied space biomedical research directed toward this specific goal. Its mission is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of long-term human presence in, development of, and exploration of space. This is accomplished by

- designing, testing and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the general benefit of mankind, including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry and the public at large in the Institute's activities and fostering a robust collaboration with NASA, particularly through NASA's Lyndon B. Johnson Space Center.

Institute Infrastructure

The NSBRI is governed by a consortium of twelve institutions — Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System, and the University of Washington. The Institute's headquarters are located in Houston at Baylor College of Medicine.

Consortium membership is not a requirement for research program participation. At present,

non-consortium institutions and laboratories lead nearly one-half of the projects funded by the Institute. The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors is responsible for assuring excellence in the Institute's intramural program through independent external peer review, and an External Advisory Council is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the research program is focused squarely on astronaut health and safety. An Industry Forum of representatives of space and biomedically-related industries assists the Institute in developing industry participation in NSBRI and in timely technology transfer. In addition to its research program, the NSBRI has developed a vital education and outreach program that takes advantage of the Institute's core research activities.

III. Specific Research Focus and Opportunity

Proposals submitted to the NSBRI in response to this NRA MUST address one of the twelve research areas discussed below. Proposals that impact more than one area should be directed to only one primary research area, although a secondary research area may be designated if the proposal has significant overlap with that area. The following subsections are meant to guide the investigator to the key problems and issues that are central to each research area. Innovative approaches to solve these problems are encouraged. Note that proposals will be evaluated for their responsiveness to the critical needs expressed in the subsections. Generally, proposals that are not responsive to these needs will not be funded.

General Information

To carry out the NSBRI's primary mission, that of designing, testing and validating effective countermeasures to address the biological and environmental impediments to human space flight (both within and beyond low-Earth orbit), the NSBRI focuses its research program on the primary needs of low-Earth orbit long-duration space flight and on the major challenges of exploration-class missions. These missions pose the greatest challenge to future space travelers, and meeting their challenge with appropriate countermeasures lies at the core of the NSBRI's responsibility. For planning purposes, a typical Mars-type exploration mission might involve trips of six months to one year each way, with a stay on Mars of one to two years. A typical long-duration space flight within low-Earth orbit might involve missions of six months or longer. In either case, effective adaptation, supported by appropriate countermeasures, is critical to a successful mission and to the long-term health maintenance of the astronauts. Potential physiological changes that may occur during prolonged space flight include, among others, significant loss of muscle and bone mass, decreased dietary intake of nutrients, profound metabolic and endocrine alterations, important changes in cardiovascular function and deleterious effects on sensorimotor performance. By addressing long-term missions of this type, increased safety, health and performance will be realized for shorter-duration space flights.

Countermeasure Readiness Levels. Since the NSBRI's primary mission concerns countermeasures, it is important to understand some of the steps involved in effective countermeasure development. These steps are called countermeasure readiness levels and are measured on a scale of 1 to 9, with the higher numbers referring to higher levels of readiness. (Investigators should read Appendix A, Section III, for a full discussion of CRLs.) As Figures 1 and 2 in Appendix A show, countermeasure development begins with basic research (levels 1 to

3), moves through countermeasure feasibility and development studies (levels 3 to 7) and ends with countermeasure ground evaluation, flight validation and operational implementation (levels 7 to 9). It is expected that the NSBRI's research program will contain studies that, for the most part, range from CRL 3 through 7.

1. NSBRI Bone Loss Team

Team Leader: Jay R. Shapiro, M.D.
Professor, Department of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road, Rm. A3068
Bethesda, MD 20814-4799
Telephone: 301-295-3600
Fax: 301-295-3557
Email: jshapiro@usuhs.mil

Weightlessness during space flight initiates a series of physiologic responses that lead to dramatic alterations in the musculoskeletal system. These include muscle atrophy that decreases muscle strain on bone, alterations in blood flow and fluid balance that alter fluid shear at the tissue level, and alterations in hormonal mechanisms controlling bone remodeling. It is well recognized that net bone loss is almost universally found in animals and humans after exposure to microgravity. Bone loss is associated with an increased risk of fracture. Less is known about the effects of weightlessness on soft connective tissues, ligaments and tendons, cartilage and the integrity of intervertebral discs. Delayed recovery of bone strength following return to Earth's gravity may perpetuate increased fracture risk and lead to skeletal fragility.

In space flight-tested rodents, bone loss occurs primarily as a consequence of depressed bone formation. In humans, increased bone resorption is primarily responsible for net bone loss. Although the magnitude of bone loss varies widely between individuals, observations of changes in bone mineral density in Mir astronauts/cosmonauts indicate that approximately 6 to 12% of bone mass may be lost during a six-month flight. Although it is recognized that muscle loss precedes loss of bone, the sequential relationships between muscle and bone loss remain poorly defined.

The research agenda for the bone loss team is set by the Critical Path Roadmap Bone Loss risks (see Appendix A, Section II) associated with long-duration space flight: acceleration of age-related osteoporosis; fracture and impaired fracture healing; injury to soft connective tissue, joint cartilage and intervertebral disc rupture with or without neurological complications; and renal stone formation. An additional important topic involves the recognized prolonged delay in the return of bone mineral density to normal following space flight, with the attendant increase in fracture risk during that period.

The current NSBRI research program includes nine projects of basic and clinical studies that share the objective of leading to countermeasure development. Details concerning the current intramural projects are provided on the Web site http://www.nsbri.org/Research/Bone.html. Two projects focus on basic mechanisms related to nutrient intake and bone mass, specifically on glucose-dependent insulinotropic peptide (GIP) and on leptin. A third project focuses on changes in estrogen and vitamin D receptor function in simulated microgravity. Other projects are concerned with fracture healing in simulated weightlessness and the effect of ultrasound on

the rate of healing, muscle-bone relationships during recovery from skeletal unloading, the efficacy of a biomechanical countermeasure to inhibit bone loss, the effects of bisphosphonate treatment on osteocyte integrity during simulated weightlessness, the study of a spinal-cord injured patient model of microgravity, and the prevention of microgravity-induced renal stone risk.

Focused Research Questions

The objective of this research solicitation is to obtain investigations that are complementary to the current research program. Thus, proposals are being sought that address three important issues: fracture and impaired fracture healing, bone mass and strength, and injury to soft connective tissue, joint cartilage, and intervertebral disc rupture with or without neurological complications. Competitive proposals should seek countermeasures that will promote normal fracture healing, restore bone lost during flight with the appropriate quantity and quality of bone, or protect soft connective tissues from injury and restore tissue integrity following prolonged space flight.

Fracture Risk/Fracture Healing. At this time, no firm data exist about the occurrence of major extremity/vertebral fractures or microfractures during, or following, extended space flight. Information is available about rates of bone loss experienced by Mir cosmonauts and astronauts. The relationship of this data to estimated fracture risk during extended space flight has not been determined. How can available data on bone loss during extended space flight be used to develop a practical estimate of fracture risk? How does weightlessness impair normal fracture healing? Are there agents that will impair or promote fracture healing during and after exposure to microgravity (e.g., cytokines/hormones acting at the tissue level, pharmacologic agents used during flight that could impair fracture healing, pharmacological agents that could promote healing, biomechanical agents that could promote fracture healing)?

Bone Mass vs. Strength and Muscle/Bone Relationship. Persistent deficits in the mechanical strength of bone may persist long after return to Earth's gravity and may lead to skeletal fragility in old age. What is the relationship between bone mass and bone strength (quantity vs. quality of bone) following real or simulated space flight? What analytical methods are available to define muscle/bone relationships? Can one develop a human model to simulate the muscle/bone relationships that exist following space flight?

Soft Connective Tissue Injury. What is the nature and incidence of soft connective tissue injury and pain during and after prolonged weightlessness or bed rest? What is the injury to cartilage, intervertebral discs, and ligaments and tendons? Are there site-specific patterns of injury to soft connective tissues? What are the gene expression patterns related to soft connective tissue injury? What is the histomorphology of the tissue response? What are the modulators of soft connective tissue injury (cytokines, growth factors and hormones)? What are the reparative processes in cartilage, intervertebral discs and tendons following injury? What are the most effective countermeasures to prevent this type of injury during or after space flight?

2. NSBRI Cardiovascular Alterations Team

Team Leader: Richard J. Cohen, M.D., Ph.D.
Whitaker Professor of Biomedical Engineering
Harvard-MIT Division of Health Sciences and Technology
Massachusetts Institute of Technology
45 Carleton Street, Rm. E25-335A
Cambridge, MA 02139-4301
Telephone: 617-253-7430
Fax: 617-253-3019
Email: rjcohen@mit.edu

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to microgravity and other factors. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. The extent of cardiovascular adaptation appears to increase with duration of space flight. The extent and implications of these adaptations for long-duration (months to years) space flight remain largely unknown. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume and a modest decrease in arterial pressure. During space flight, the cardiovascular system is not subjected to the stresses associated with changes in posture in a gravitational field. In addition to microgravity, space flight is associated with other physiologic stressors such as sleep disruption, confinement and other environmental alterations that may also adversely affect cardiovascular structure and function.

Long-duration space flight leads to the development of orthostatic intolerance upon reentry, may cause a reduction in cardiac mass, and might alter susceptibility to heart rhythm disturbances. In addition, long-duration space flight affects cardiovascular response to exercise and may in principle lead to the manifestation of previously asymptomatic cardiovascular diseases.

The objectives of the NSBRI Cardiovascular Alterations Team are to

- characterize and quantify the adverse effects of space flight on cardiovascular structure and function;
- determine the mechanisms of these adverse effects;
- develop effective countermeasures to these adverse effects; and
- develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth.

These research objectives are driven by the Critical Path Roadmap Cardiovascular risks (see Appendix A, Section II) associated with long-duration space flight: impaired cardiovascular response to orthostatic stress, occurrence of serious cardiac dysrhythmias, diminished cardiac function, manifestation of previously asymptomatic cardiovascular disease, and impaired cardiovascular response to exercise stress.

The current research program involves nine ground-based projects and two potential space-flight studies. Details concerning the current intramural projects for this team are provided on the Web site http://www.nsbri.org/Research/Cardio.html. Many of the projects impinge on more than one critical risk. The strategy of the cardiovascular team is to have a dynamic interplay between

projects focused on studies in animals, humans and computer simulations. Part of the strategy is to develop new technologies to be used in the studies which also have applications for astronaut monitoring and therapy and spin-off applications on Earth. The primary focus of the team has been on the problem of postflight orthostatic hypotension. In addition, several of the projects deal with the issue of cardiac arrhythmias in space and with the risk of diminished cardiac function.

Focused Research Questions

The objective of this research solicitation is to add investigations that are complementary to the current research program and fill in the gaps in that program. Thus, proposals are being sought that specifically address the following risks:

Diminished Cardiac Function. Proposals are solicited that address the relationship between cardiac atrophy and central or peripheral cardiovascular function (e.g., changes in cardiac systolic and diastolic function that could lead to orthostatic hypotension). These studies may include animal or human studies. Proposals that specifically identify and test countermeasures are preferred.

Manifestation of Previously Asymptomatic Cardiovascular Disease. Proposals that address this critical risk may focus on methods to identify individuals for the presence of *silent* cardiovascular disease that may manifest itself during space flight. Proposals may also address whether and by what specific mechanisms space flight may accelerate such cardiovascular disease processes.

3. NSBRI Human Performance Factors, Sleep, and Chronobiology Team

Team Leader: Charles A. Czeisler, M.D., Ph.D.
Professor of Medicine, Harvard Medical School
Chief, Division of Sleep Medicine, Brigham and Women's Hospital
221 Longwood Avenue, Room 438A
Boston, MA 02115
Telephone: 617-732-4013
Fax: 617-732-4015
Email: caczeisler@rics.bwh.harvard.edu

The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During long-duration space flight, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under space flight conditions. This team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: weightlessness (microgravity), altered light-dark cycles, altered or reduced sleep/rest opportunities, high levels of automation, and habitation in a remote, inaccessible location. The primary thrust of the team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during long-duration space flight.

The goals of the Human Performance Factors, Sleep, and Chronobiology Team are to:

- characterize and quantify the adverse effects of long-duration space flight on sleep and circadian rhythmicity;
- characterize and quantify the effect of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance;
- understand the basic mechanisms underlying the deterioration of sleep, circadian organization and human neurobehavioral function during space flight;
- develop high-fidelity mathematical models of performance based on circadian organization and sleep-wake history;
- develop effective countermeasures to optimize sleep and facilitate circadian adaptation in space and thereby maintain optimal neurobehavioral performance; and
- develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight, with possible spin-off applications on Earth.

These research objectives are driven by the Critical Path Roadmap risk (see Appendix A, Section II) related to human performance failure because of sleep and circadian rhythm problems.

The current research program involves nine ground-based research projects. Details concerning this program are provided on the Web site http://www.nsbri.org/Research/Sleep.html. Although the focus of the team is on a single risk, many of the projects impinge on more than one critical risk. The team strategy is to develop a synergistic interaction between research projects at the molecular, cellular, organismic and human levels; and to integrate predictive biomathematical modeling of the sleep and circadian systems into the fabric of the program.

Focused Research Questions

The objective of this research solicitation is to obtain investigations that are complementary to the current research program and fill in gaps in that program. Thus, proposals are being sought that specifically address the following research topics:

Physical Effects. Proposals are sought to determine how the factors associated with space flight, including stress, diminished sleep opportunities, and circadian disruption, affect sleep- and/or circadian-mediated neuroendocrine, metabolic, neurologic or autonomic functions, particularly how those factors increase the biomedical risks of space flight during extended-duration missions. How do individual characteristics alter the responses to these factors?

Novel Countermeasure Development. Proposals are sought to determine how recent advances in the neurobiology of sleep and/or circadian rhythms (e.g., orexin/hypocretin system, circadian photoreception, output pathways for regulation of sleep or circadian rhythms) can be used to develop countermeasures to facilitate adaptation to the space environment and thereby maintain optimal neurobehavioral performance during an exploration-class space mission.

4. NSBRI Immunology, Infection, and Hematology Team

Team Leader: William T. Shearer, M.D., Ph.D.
Professor of Pediatrics and Microbiology & Immunology
Baylor College of Medicine
6621 Fannin, MC 1-3291
Houston, TX 77030-2399
Telephone: 832-824-1274
Fax: 832-825-7131
Email: wshearer@bcm.tmc.edu

For 40 years, biomedical researchers have been attempting to gather definitive information on the possible development of a secondary immunodeficiency due to conditions of space travel. Although definitive information is yet to be obtained, past and present research demonstrates that the conditions that humans face in long-term space flight have an impact upon the immune system. For example, radiation of the type found during a space flight is known to induce changes in host resistance so that, in time and without proper shielding and other precautions, infections and malignant cells gain the advantage and conquer the host. Other important conditions that pose risks for astronauts are weightlessness, confinement in a restricted space, stress, isolation, microbial contamination, and sleep deprivation. Clinical observations with patients undergoing immune suppression and model studies with humans and animals document the importance of a sufficient level of immune function to protect against the consequences of early cell death, reactivation of latent viral infections, and development of malignancies. The science of space immunology, therefore, is founded upon well-received principles and assumptions that prescribe a need for well-planned and executed experiments capable of predicting the risks to the human immune system in long-term space travel and for an active countermeasure development program designed to reduce the risks to the immune system to an acceptable level.

Because stress is almost a constant condition of space flight, investigators have sought to establish a model where the same type of stress could be experienced by a large number of subjects at the same time. Models studied to date have included medical students taking examinations, subjects during heavy exercise, humans exposed to high altitudes, isolation, and sleep deprivation, and the head-down bed rest model that simulates several conditions of space travel. Some of these model studies suggest that serious consequences could result from possible immune system aberration during long-term space travel.

Space-based countermeasure development in this area is still at the research level. Because of the four-decade-long experience with humans who have congenital immunodeficiencies and the nearly 20-year history of coping with the best understood secondary immunodeficiency, AIDS, considerable progress has been made in restoring immunity and preventing it from being damaged. Restoration of humoral immunity can be accomplished with immunoglobulin treatments, and bone marrow stem cells can replace defective or damaged stem cells and their immune system descendants. Vaccines have for decades prevented human infection, and simple measures such as adequate nutrition and proper sleep have enabled humans to avoid serious complications of intercurrent infections. Application of these measures to restore immunity or even prevent immune damage in space is a high priority of the Institute's research program.

The Critical Path Roadmap risks (see Appendix A, Section II) in this area are increased risk of infection due to impaired immune response, altered environmental exposure, and persistent viruses or the reactivation of viruses; increased risk of carcinogenesis due to increased radiation-induced or cell-mediated oncogene expression, decreased immune system surveillance, and reactivated viruses; altered hemodynamics and cardiovascular dynamics caused by altered blood components; altered wound healing caused by altered immune cell function or altered local tissue transport properties; altered host-microbial interactions resulting from changes in microflora, alterations in host susceptibility, or genetic changes or mutations of microorganisms; and increased risk of allergies and hypersensitivity reactions.

The current research program in this area consists of six projects described on the Web site http://www.nsbri.org/Research/Immune.html. These projects use various model systems, including irradiated and hind-limb suspended animals, to examine latent virus activation, stem-cell alteration, mucosal immune and HPA-axis responses and apoptosis of T cells, etc., during space flight. One project focuses on microbe contamination of a spacecraft. There is a high degree of overlap among these projects. For example, altered microbes and increased susceptibility to infection caused by space conditions are among the interests of all six projects, and neuroendocrine abnormalities are a subject of five of the projects.

Focused Research Questions

Proposals are being sought in three areas: the types of altered immune function that occur in space, the possible increased risk of allergies and hypersensitivity reactions that may occur in space; and the development of specific, targeted countermeasures that would reduce the risks associated with this research area.

Altered Immune Function. How do the various factors associated with space flight (e.g., radiation, physical and psychological stress, confinement, weightlessness, etc.) affect immune function, cancer risk, susceptibility to microbial infections, latent virus reactivation, stem cell/progenitor cell biology and function, mucosal immunity, etc.? Do alterations in the body's systems in these areas during space flight pose significant risks to crewmembers? Are there assays that reliably predict changes in these systems, and can these assays be adapted to space travel?

Allergies and Hypersensitivity Reactions. Do unique environmental factors inside the spacecraft promote the transmission and activity of microbial pathogens or cause increased risk of infection, autoimmunity, allergy or hypersensitivity reactions independent of altered immune function? How would altered immunity in space, if it occurs, affect the development of allergies, hypersensitivities and autoimmune diseases?

Countermeasure Development. Are there countermeasures that would remove the immune-specific risks associated with space flight (see the Critical Path Roadmap risks listed above) or reduce these risks to acceptable levels?

5. NSBRI Integrated Human Function Team

Team Leader: Martin J. Kushmerick, M.D., Ph.D.
Professor of Radiology, Physiology & Biophysics and Bioengineering
Department of Radiology, AA-010K HSC
University of Washington
1959 N.E. Pacific Street, Box 357115
Seattle, WA 98195-0001
Telephone: 206-543-3762
Fax: 206-221-6515
Email: kushmeri@u.washington.edu

This research area seeks to integrate knowledge from the other discipline research areas, enabling an understanding of overall human function and leading to a reliable evaluation and prediction of an astronaut's safety and functional capacity during an extended space mission. Thus, the goals of this program are to develop the general methodology necessary to integrate the variety of physiological research findings emanating from different laboratories, thereby advancing the description and understanding of human systems and their parts; to improve the ability to predict human responses to functional stresses, especially those encountered in long-duration space flight; and to assess the potential efficacy of countermeasures in reducing the risks involved in space flight. The loss of homeostasis and/or appropriate dynamic responses under stress likely involves the interaction of varied human functions and mechanisms at many levels (e.g., molecules to organ systems). Because of genetic and experiential differences among individuals, the methodology developed to enable integration needs to address generic human responses as well as individual functional characteristics. Successful projects should develop algorithms and concepts that specify how integration of the sub-components in a hierarchy of complex component interactions could be accomplished. The term *"Digital Human"* captures this vision and goal in a simple yet profound way.

There are six projects in the current program. Details concerning these projects are available on the Web site http://www.nsbri.org/Research/Integrated.html. All focus on metabolism and on cardiac and skeletal muscle at the level of molecular, cellular, and organ properties. Each demonstrates a desirable balance of experimental work and synergistic modeling in the areas of cell electrical properties, control of intracellular calcium dynamics, cross-bridge properties in different cell types; cellular energy metabolism, whole-body substrate distribution and metabolism that may be altered during space travel, and convergence of cellular to organ mechanics.

Focused Research Questions

Proposals are sought that will create analytical and predictive models and enable simulations that answer questions involving multiple human subsystems. Such models will integrate human function across multiple scales of organization and widely varying time scales, using both vertical (hierarchical) and horizontal integration involving such diverse organizational scales as molecule, cell, tissue, organ, and organism. It is anticipated that these projects will involve interplay between fundamental mechanistic and phenomenological analyses. Projects must be stronglyrelated to experimental data but may or may not involve new experimental work. In order to be considered for funding, proposals must address one of the following areas.

Neuroendocrine Model Development. This project should develop an integrative approach to modeling human neuroendocrine function, including important elements of metabolism and nutrition. The model should take into account global and intermediary metabolism, cell cycle control, pituitary-hypothalamus and peripheral interactions, common endocrine interactions with a range of body functions, and physiological and psychological stresses.

Musculoskeletal Model Development. This project should focus on developing an integrative approach to modeling the interaction between bone and muscle in humans, with a view to simulating the atrophy and bone loss that takes place during musculoskeletal unloading and the restoration that takes place during reloading. The model should represent the role of limb mechanical effects (loads and stresses) integrated with bone, muscle and tendon properties, as well as calcium metabolism, and effects of parathyroid hormone and vitamin D.

6. NSBRI Muscle Alterations and Atrophy Team

Team Leader: Kenneth M. Baldwin, Ph.D.
Professor, Department of Physiology & Biophysics
University of California, Irvine
Medical Sciences I, Rm. D340
Irvine, CA 92697-4560
Telephone: 949-824-7192
Fax: 949-824-8540
Email: kmbaldwi@uci.edu

Human and animal research clearly indicates that the skeletal muscle system is negatively impacted by prolonged exposure to the unloading involved in space flight and bed rest in humans and tail-suspension in animals. The following critical deficits have been identified as important to counteract during extended space flight: reduced muscle mass (atrophy), which is thought to be due to an imbalance in protein synthetic to protein degradation activity within targeted fibers (the mechanism for such a response is largely unknown); reduced muscle strength leading to a decrease in physical-activity performance and high power-output capacity (deficits in strength often exceed the loss in muscle mass, suggesting that complex mechanisms are responsible for the reduced performance); a slow-to-fast shift in the contractile protein phenotype (e.g., shifts to faster myosin heavy chain [MHC] and calcium-cycling proteins) inducing muscle fibers to become less economical in sustaining force output; a decreased resistance to fatigue, which could have functional implications in the performance of extravehicular activity in space and in performing emergency egress activity upon spacecraft landing; a proneness to muscle injury, which is due to the atrophy and loss of strength with increased susceptibility to accidents that could cause damage to other systems (e.g., bone fractures); changes in muscle properties that are closely linked to changes in the ability of the nervous system to accurately control movements, thereby affecting safety when performing any type of work.

The Critical Path Roadmap risks (see Appendix A, Section II) in this area are closely associated with the loss of skeletal muscle mass, strength and endurance; inability to adequately perform tasks due to motor performance, muscle endurance, and disruption in structural and functional properties of soft and hard connective tissues of the axial skeleton; inability to sustain muscle performance levels to meet the demands of performing activities of varying intensities; propensity to develop muscle injury, connective tissue dysfunction and bone fractures due to

deficiencies in motor skill, muscle strength and muscle fatigue; and the impact of deficits in skeletal muscle structure and function on other systems.

The current NSBRI research program includes eight projects closely aligned with addressing issues relevant to the critical path. Details concerning the research program are provided on the Web site http://www.nsbri.org/Research/Muscle.html. Each project addresses key fundamental issues and questions directly related to human health, performance and safety during long-duration space flight. However, the program lacks a robust research effort using human subjects, does not address issues related to the effect of altered loading on muscle and sensory-motor function, and does not adequately explore non-exercise (e.g., artificial gravity) countermeasures.

Focused Research Questions

Loading/Unloading Human Skeletal Muscle. How do altered loading states and paradigms of resistance training influence molecular and cellular processes that impact protein turnover in human muscle fibers? Are there synergistic effects when various activity paradigms are carried out simultaneously with other countermeasures, such as nutritional modification and pharmacological intervention?

Muscle Loading and Sensory-Motor Function. How do altered loading states affect sensory motor processes that affect posture, balance and the performance of locomotor tasks of varying intensity and complexity?

Artificial Gravity and Muscle Function. How does artificial gravity (e.g., gravity-equivalent acceleration and variable-G forces) affect the structure and function of human skeletal muscle in normal and atrophying skeletal muscle, as well as other systems impacted by microgravity?

7. NSBRI Neurobehavioral and Psychosocial Factors Team

Team Leader: David F. Dinges, Ph.D.
Professor of Psychology in Psychiatry and Chief, Division of Sleep and Chronobiology
Department of Psychiatry
University of Pennsylvania School of Medicine
423 Guardian Drive, 1013 Blockley Hall
Philadelphia, PA 19104-6021
Telephone: 215-898-9949
Fax: 215-573-6410
Email: dinges@mail.med.upenn.edu

The success of long-duration missions, particularly exploration missions, will depend heavily on prevention, identification, and mitigation of neurobehavioral and psychosocial risks to crew health, safety, and productivity. Astronauts aboard exploration missions will endure behavioral challenges for a much longer period of time than have ever been experienced during space flight. Stressors and risk factors on these missions include confinement for up to three years with the same small group of people; isolation from family and friends; limited communication with Earth, including as much as a 24-minute delay in bi-directional communications; and loss of privacy due to habitability constraints. There are also risks to neurobehavioral capability and emotional stability posed by prolonged weightlessness, enhanced radiation exposure, physical

illness, interpersonal strife, and equipment failure in space. Language, culture, gender, and work role differences will also pose challenges to crew communication and effectiveness. Without mitigation, these stressors individually and collectively have the potential to erode cognitive performance; change neuroendocrine, cardiovascular, and immune responses; disrupt appetite, sleep, and other basic regulatory physiology; lead to neuropsychiatric impairment through anxiety and depression; and potentiate serious interpersonal problems among crewmembers.

This research area is concerned with developing novel ways to monitor individual astronaut brain functions, as well as group behaviors, and to provide preventive and operational countermeasures to enhance crew performance, motivation, and quality of life. The scope of this area fits within the Critical Path Roadmap risks for Human Performance (see Appendix A, Section II): identification of the neurobehavioral and psychosocial risks to crew health, safety, well being, performance, and productivity during long-duration space missions; evaluation of the effects of space-related stressors (i.e., habitability constraints, microgravity, radiation, work requirements, sleep deprivation, perceived risks, restricted communication with Earth and boredom) on physiological and psychological functions of individuals and crews; development of accurate, practical techniques and approaches to monitor behavior and performance capability during missions; development and validation of countermeasures to manage or mitigate space-related risks to neurobehavioral functions and to enhance health, motivation, safety, and performance during such missions; identification of strategies to maintain motivation and ensure an effective quality of life in space; and development of procedures to determine optimal leadership style, crew composition, organization, and communication with Earth.

The team's initial strategic research agenda involves eight ground-based studies that collectively address four thematic questions. Details concerning the current program are provided on the Web site http://www.nsbri.org/Research/Psycho.html. Questions addressed by the current projects include

- What are the effects of culture, personality and leadership on performance, stress and health in isolated groups?
- What are the major influences on interpersonal actions, communications and problem solving in small groups?
- How can affective, neurobehavioral and neurocognitive dysfunction be objectively detected in remote locations?
- What neurobiological processes of stress and arousal are the optimal targets for behavioral and pharmacological interventions?

Focused Research Questions

Proposals are being sought that address one of the following questions.

Neurobehavioral and Psychosocial Responses to Space Flight. What are the effects of long-term exposure to the major factors in the space environment on emotions (including emotional reactivity, stress neurobiology and responses, modulation of mood, and vulnerability to affective disorders), cognition and performance (including processes of sensation and perception, learning, vigilance, problem solving, decision making, and motor skills), and behavioral health?

Novel Countermeasure Development. How can novel neuroscience technologies (e.g., neuroimaging via fMRI, MRS, PET, NIR; transcranial magnetic stimulation) or novel behavioral methodologies (e.g., virtual reality, prolonged behavioral monitoring, and experimental manipulation of small group microsocieties in isolation and in tandem) be used to develop

countermeasures for the psychosocial and neurobehavioral effects of prolonged space flight?

Performance Strategies. What are the behavioral strategies, scheduling strategies and habitat design elements that can maintain or enhance crew performance and prevent the development of hostility between crews and ground-support personnel during long-duration space flight?

8. NSBRI Neurovestibular Adaptation Team

Team Leader: Charles M. Oman, Ph.D.
Senior Research Engineer and Director, Man-Vehicle Laboratory
Department of Aeronautics and Astronautics
Center for Space Research, Massachusetts Institute of Technology
77 Massachusetts Avenue, Rm. 37-219
Cambridge, MA 02139-4301
Telephone: 617-253-7508
Fax: 617-258-8111
Email: cmo@space.mit.edu

The most overt change affecting an astronaut in space flight is the immediate response of the neurovestibular system to weightlessness (traditionally called a gravitational change). Initially, problems arise when astronauts transition to a weightless condition (from 1 G to 0 G), unfortunately at a time when physical and cognitive performance is often critical for mission success and safety. Problems appear again at the end of a mission, during and following a return to Earth (from 0 G to 1G). Postflight problems have generally been more severe after three-to-five month Mir and International Space Station (ISS) flights than on typical one-to-two week Shuttle missions, showing that, for some components of the vestibular system, adaptation to 0 G takes place over time scales of months, rather than weeks. Looking beyond ISS to interplanetary exploration missions, one can anticipate operationally significant vestibular problems when astronauts make the transition from 0 G to partial G, or from 0-G to an artificial gravity environment.

During the 1980s and ’90s, space neurovestibular research largely focused on understanding the effects of otolith weightlessness on the vestibulo-ocular reflex (VOR) and on attempting to predict space sickness susceptibility. Today, the research agenda is set by the Critical Path Roadmap Neurovestibular Adaptation risks (see Appendix A, Section II) associated with long-duration space flight: disorientation and reduced performance on cognitive and physical tasks, including vehicle egress, especially during/after G-level changes (associated with acute spontaneous, and head-movement-contingent vertigo, nystagmus, oscillopsia, saccadic errors, and reduced dynamic visual acuity); impaired neuromuscular coordination strength upon return to positive G leading to increased incidence of falls and injury during emergency egress and escape (gait ataxia, postural instability); impaired cognitive and/or physical performance due to spatial disorientation; motion sickness symptoms or treatments (including short-term memory loss, reaction time changes, drowsiness, fatigue, torpor, irritability, and ketosis) as a result of changes in G level or use of artificial gravity; autonomic dysfunction (including cardiovascular, respiratory, gastrointestinal, sleep, and mood changes), which may be of vestibular origin; and permanent impairment of orientation or balance function due to microgravity or radiation (causing chronic imbalance, gait ataxia, vertigo, eye movement disorders, chronic vestibular insufficiency, and poor dynamic visual acuity). Thus, NSBRI’s neurovestibular adaptation research program supports research aimed at developing scientifically-based countermeasures

against the vestibular problems associated with space flight: space motion sickness, disorientation, oculomotor deficits, postflight postural instability, and gait ataxia.

The current research program involves seven ground-based projects; details concerning these projects are provided on the Web site http://www.nsbri.org/Research/Neuro.html. Six of the projects focus on the highest priority critical path risk (disorientation and reduced performance on cognitive and physical tasks) while one or two projects focus on the other risks. No project addresses the fourth risk, autonomic dysfunction, which may be of vestibular origin.

Focused Research Questions

This research solicitation seeks investigations that are complementary to the current team portfolio and that collectively address four of the five critical path risks. Thus, proposals are being sought that specifically address the following risks.

Vestibular/Autonomic/Emetic Physiology. What is the physiological basis for the "sensory conflict" theory for motion sickness? What is the locus and function of the putative "conflict" signal? What is the neural or chemical linkage between balance and emetic centers? What mechanisms establish the threshold for nausea and emesis? What neurotransmitter and receptor systems are involved? Is the physiology of space motion sickness fundamentally different from other forms of motion sickness? Can more effective anti-motion sickness drugs be developed which target emetic centers or the vestibular-emetic linkage? Drugs must be effective, easily and safely used over days to weeks with minimal side effects and must not impair neurovestibular adaptation. Can improved anti-motion drug delivery systems and dose and side effect monitoring systems be developed? What are the best ground-based techniques for evaluating 0 G pharmacokinetics and for assessing the effectiveness and side effects of drug countermeasures?

Postflight Neurovestibular Function. Does the neurovestibular response to weightlessness impair postlanding cardiovascular regulation and contribute to orthostatic intolerance? How is it mediated? Can an effective countermeasure (e.g., artificial gravity) be developed to exploit this knowledge? What are the relative contributions of neurovestibular adaptation, neuromuscular deconditioning and cardiovascular deconditioning during space flight to the postflight problems of neuromuscular coordination, ataxia and locomotion? What is the effect of possible cardiovascular, muscular and skeletal rehabilitation therapies on neurovestibular recovery? Can somatosensory information be used effectively to accelerate postflight neurovestibular readaptation?

9. NSBRI Nutrition, Physical Fitness and Rehabilitation Team

Team Leader: Joanne R. Lupton, Ph.D.
Regents Professor and William W. Allen Endowed Chair in Human Nutrition
Texas A&M University
218 Kleberg Center, MS 2471
College Station, TX 77843-2471
Telephone: 979-845-2142
Fax: 979-862-2378
Email: jlupton@tamu.edu

An individual's mutually interdependent nutritional status and level of physical fitness affect the physiological function of all of the body's systems. Optimum astronaut performance during space flight requires that these systems be maintained at an appropriate level of function, with appropriate reserves to enable astronauts to respond to the special challenges that arise during and just after a mission. The primary foci of this research area are the critical needs for adequate nutrition during a long-duration space flight simultaneous with a prescribed use of exercises to maintain appropriate fitness. Since physical activity will, in part, determine nutrient needs, and since the optimization of nutrient delivery will, in part, depend upon blood flow and muscle mass, which are both affected by physical activity, these two disciplines need to be considered together.

The critical issues for nutrition are counteracting the observed anorexia of space flight; determining nutrient needs to meet the modified requirements obtained during space flight, with stressors that include weightlessness and a different radiation environment; and developing new nutritional strategies, including the use of functional foods, supplements, and the timing of food intake relative to the specific prescribed exercise activities that will optimize human performance.

The critical issues for physical fitness include developing appropriate aerobic and resistive exercises that will prevent or reduce some of the physiological changes during space flight; determining the mode, frequency, duration, and intensity for each exercise; and defining the appropriate individual exercise prescription; determining the optimal timing of exercise components with respect to food intake and other activities; and developing the hardware to most efficiently implement the exercise countermeasures.

Although the Critical Path Roadmap (see Appendix A, Section II) contains specific risks associated with food and nutrition, the risks that may be ameliorated by nutritional and exercise-related interventions are reduced cardiovascular capacity, loss of bone mineral density, diminution of skeletal muscle function, depressed immune response, radiation-enhanced development of cancer, decrease in cognitive function, alterations in sleep patterns, and neurobehavioral and psychosocial risks.

The nutrition and physical fitness program presently consists of three nutrition countermeasure projects and one potential space-flight physical fitness project. Details concerning these projects are provided on the Web site http://www.nsbri.org/Research/Nutrition.html.

Three of the four projects involve countermeasures to the same critical problem: muscle wasting. The combination of muscular inactivity and stress during space flight results in a loss of skeletal muscle mass that leads to decreased muscle strength, which may compromise crew capabilities. A bed rest study will determine whether an amino acid supplement can ameliorate these negative effects by increasing protein synthesis. A bioreactor cell culture project, which addresses myocyte response in an *in vitro* model, will use the same amino acid supplement as the bed rest study and address mechanisms of insulin secretion. The physical fitness countermeasure should enhance the nutritional countermeasure by increasing blood flow to muscle and also by maintaining muscle strength.

Focused Research Questions

The objective of this research solicitation is to fill in gaps and strengthen the current research program. Proposals are requested that specifically address the following focused research questions.

Exercise Countermeasures. Without routine aerobic exercise during long-duration space missions, there is a decrease in intensity and endurance of aerobic capability as measured by oxygen consumption (VO_2 max) and heart rate per energy exerted (watts). Resistive exercise is required for maintenance of muscle performance as measured by strength and endurance. Muscle atrophy and loss of force and power have been documented through muscle biopsies. The primary goal of research in this area should be to study the effectiveness of exercise countermeasures to ameliorate the above undesirable effects of space flight. End points should include parameters quantifying the cardiovascular response, bone metabolism, body composition, and skeletal muscle metabolism and function. The exercise countermeasures must utilize approaches applicable or relevant to space flight, and the study design must include strict dietary control and contain measures of energy balance. It is expected that implementation of a successful proposal will require coordination with the currently funded bed rest and nutritional study.

Appetite and Thirst Controls. In spite of adequate provision of food and water, inadequate food intake is characteristic of human space flight. This reduction of food intake translates into a significant energy deficit with resultant loss of body mass and diminution of physical fitness. Suboptimal intake of essential macro and micronutrients and inadequate water intake also occurs. It is thought that alterations of central and peripheral appetite and thirst homeostasis underlie these perturbations. Proposals in this area should be aimed at understanding underlying mechanisms and designing effective nutritional countermeasures to these deficiencies in nutrient intake.

Alterations in Nutrient Partitioning and Metabolism as a Function of Weightlessness and/or Other Space Flight Stressors. For crewmembers, space flight appears to increase resting metabolic rate in the presence of chronic stress and increased protein turnover. Limited data suggest insulin insensitivity and increased fat oxidation occur. Examples of other changes occur with iron and calcium. Red cell mass is decreased by 10-15% during space flight resulting in the release of additional iron, a strong pro-oxidant, suggesting that it might be prudent to reduce dietary iron intake. These changes raise important questions in humans regarding the identification of nutritional countermeasures to combat the detrimental alterations in body composition and nutrient partitioning (e.g., bone, muscle, and adipose tissue) as well as in associated organ systems. It is likely that these effects reflect alterations in systems coordination as well as individual cell function. These manifestations may relate to direct influences of microgravity or other as yet undefined space flight stressors. Proposals focused on this area should aim at the development of countermeasures to ameliorate the above detrimental alterations in nutritional physiology and biochemistry.

Meal Allocation: Nibbling vs. Meal Eating, Supplements vs. Whole Meals, Timing of Nutrient Intake. The timing and frequency of meals with respect to activity, including sleep cycles and exercise, and to the most effective utilization of nutrients may be a key factor in maximizing astronaut health on long-duration space flights. For example, aerobic exercise has been shown to increase blood flow, which could benefit the uptake of amino acids into muscle if the amino acids were provided at the time of maximal blood flow. Similarly, after a substantial meal, there is a depression in protein synthesis. Since total body protein synthesis decreases in

space flight, perhaps supplements between meals of amino acids in addition to the protein in three meals may be the most effective food pattern to enhance muscle protein synthesis and consequently maintain muscle function. For another example, extravehicular activity (EVA) often requires 7-9 hour periods of highly focused activity with no intake but water. Determination of specific nutrients (both type and amount) and timing of ingestion to maximize mental and physical performance for these tasks would enhance crew safety and performance. Proposals focused on this area should focus on meal patterns, distribution of nutrients, and the timing of meals or supplements in relationship to maximum utilization of nutrients, physical activity, and assigned tasks.

10. NSBRI Radiation Effects Team

Team Leader: John F. Dicello, Ph.D.
Professor of Oncology
The Johns Hopkins Oncology Center, Johns Hopkins University
Harry and Jeanette Weinberg Bldg., Rm. 1440
401 N. Broadway
Baltimore, MD 21231-8922
Telephone: 410-614-4194
Fax: 410-502-1419
Email: diceljo@jhmi.edu

Exposure to higher than normal radiation levels is one of the major health risks to humans on long-term space flights. This exposure results primarily from galactic cosmic rays (GCR) and solar particle events. The protons and high Z, energetic particles (HZE) involved may exert sizable biological effects even at low fluence, and there are considerable uncertainties associated with secondary particle effects (e.g., HZE fragments, neutrons, etc.). Although the health risks from exposure to radiation (x-rays, gamma rays or electrons) encountered on Earth are comparatively well-known, the health risks from space radiation are not well-known. The space-related risks are summarized in the Critical Path Roadmap for the radiation effects area (See Appendix A, Section II): cancer induction; central nervous system (CNS) damage from ionizing radiation; synergistic effects resulting from simultaneous exposure to radiation, weightlessness, and other spacecraft environmental factors (e.g., cytotoxic compounds present in the spacecraft); acute effects resulting from damage to the nervous system, intestinal tract, and blood-forming organs; and the effects of space radiation on fertility, sterility, and heredity.

The current NSBRI radiation research program involves six ground-based projects, details of which may be found on the Web site http://www.nsbri.org/Research/Radiation.html. A major component of the program is focused on one model system, the Sprague-Dawley rat, and one major endpoint, mammary tumorigenesis. The biological endpoint being addressed is cancer. In addition, two projects address CNS damage, one addresses genetic damage, and one addresses possible nutritional countermeasures to space radiation.

Focused Research Questions

Each application must provide a strategy and schedule that would describe how the results of the proposed experiments would finally yield data that could be used directly for providing a quantitative estimate of risk or for producing an effective countermeasure. It is important that this strategy be as explicit as possible and contains a schedule that would yield results within the

necessary time frame. The objective of this NRA is to solicit new research investigations that augment the existing radiation team's program. In particular, proposals are being sought that specifically address the following.

Improving the Predictions of Risks to Human Health from Space Radiations. What is the proper methodology to extrapolate the biological results of experimentation to human risk? How can existing epidemiological data for humans be utilized to interpret biological data in terms of risk assessments for exposures in space? What are the methodologies required to extrapolate biological results to low-dose risk predictions? Are the risks from the various radiations in space independent? What is the dependence of the biological response on fluence and fluence rate? Are the single-particle events from the HZEs in space properly simulated with present accelerator-based exposures?

Providing Effective Countermeasures that Will Significantly Reduce these Risks. The countermeasures referenced here are biological or biochemical agents useful for modulation of significant radiation effects, which offer substantial promise as prevention or countermeasure tools to reduce or minimize human risk arising from space-radiation exposures. Proposed agents shall have demonstrated efficacy for chemoprevention of malignancies with low or no significant toxicity. Radiation countermeasure agents shall be based on scientific understanding of their likely efficacy against protons and high energy, highly charged nuclei (HZE particles). With this in mind, are there chemical or biological agents that can be implemented to mitigate radiation risks? Are there radioprotectants that mitigate acute exposures? Are there classes of minimally toxic agents that will globally reduce radiation risks?

11. NSBRI Smart Medical Systems Team

Team Leader: Jeffrey P. Sutton, M.D., Ph.D.
Director, Neural Systems Group
Massachusetts General Hospital
Harvard-MIT Division of Health Sciences and Technology
Bldg. 149, 13th Street, 9th Fl.
Charlestown, MA 02129-2000
Telephone: 617-726-4350/731-2388
Fax: 617-726-4078 FAX
Email: sutton@nmr.mgh.harvard.edu

Research in this area is focused on the ultimate development of an advanced, integrated, and autonomous system for astronaut health assessment, maintenance, and medical care. This system would include subsystems for the delivery and evaluation of medical interventions and other countermeasures that reduce the deleterious effects of space travel and enhance the overall well being of astronauts. The scope of research in this area includes new types of biometric sensors; novel medical and surgical techniques; robotic medical assistance systems; advanced drug synthesis and delivery systems; smart algorithms for medical data systems; automated decision support for training and care; and systems-engineered platforms for sensor, algorithm, and effector integration.

Although this research area is concerned with most of the risks related to the clinical capabilities component of the Critical Path Roadmap (see Appendix A, Section II), its scope is significantly

wider. The current program is accessible at http://www.nsbri.org/Research/Med_Sys.html and consists of eight multi-disciplinary projects that integrate engineering, computation and biomedicine with innovation in technology and medical care. These projects address the following general topics: novel sensor systems for monitoring and diagnosis, novel three-dimensional imaging strategies, novel therapeutic modalities and intelligent systems for mentoring and training.

Focused Research Questions

There are several gaps that exist in the current program, and the objective of this solicitation is to fill some of them with projects that are complementary to the currently funded set. Specifically, projects are sought that address the following topics.

Decision Support System for Monitoring. Formalized approaches are needed to decide how changes in measured data should be integrated and brought to the attention of crew and/or ground support personnel. These approaches require domain-specific models of both short- and long-term changes in physiological status and status of the crew's environment and life support systems. Computational techniques are required to direct monitoring systems, allocate monitoring resources across systems, and determine when, to whom, and how urgently to report monitoring results. Communication latencies, dropouts and limited bandwidth introduce unavoidable disturbances. System architectures and collaborative approaches therefore need to be developed to support the requirement for shared decision-making and data management.

Decision Support Systems and Knowledge Bases for Diagnosis and Treatment. Physiological monitoring and medical care in a remote, isolated environment will depend on automated and semi-automated processes, alerts and reminders, and methods for aiding human decision makers. This, in turn, requires the ready availability of medical knowledge resources, including textbooks, atlases, guidelines, formularies, diagnostic decision aids, and other tools. Methods for organizing and retrieving knowledge relevant to a medical problem, inferring conclusions, developing and customizing diagnostic and treatment plans, and monitoring responses are needed.

Novel Therapeutic Modalities. Recognizing that facilities and specialty expertise for treating illness and injury will be limited, research is needed to identify alternative approaches that emphasize less invasive therapeutic interventions. Methods and devices that can be used by individuals with limited expertise under adverse space-flight conditions are required. The focus should be on approaches that minimize resource requirements and restore functionality, allowing mission completion.

12. NSBRI Technology Development Team

Team Leader (Acting): Jeffrey P. Sutton, M.D., Ph.D.
(See Section 11)

The goal of this research area is to develop technologies that support the ground-based or space-flight research mission of the NSBRI. Thus, this team creates systems and tools such as sensors, instruments, devices, and intelligent software that can support the other NSBRI Research Teams and the space life science research community at large. The tools and technologies developed

through this program can be used for human or animal studies, countermeasure development or application, and medical care. Generally, the requirements for these tools and technologies are predicated on the carefully developed needs of the other research teams. These projects should support the investigation of the effects of space flight on human physiology and behavior; apply this information toward the development of techniques, technologies, instruments, and countermeasures that will sustain humans during future long-duration space missions; and benefit the quality of life and medical care on Earth.

The current program consists of eight multi-disciplinary projects that identify, integrate, and apply scientific and engineering technology to the research and development needs of the other NSBRI teams and the entire space flight community working on countermeasures. The currently funded projects are strongly related to the activities of nine other NSBRI research areas. Details concerning the current program are provided on the Web site http://www.nsbri.org/Research/Tech.html.

Focused Research Needs

The objective of this solicitation is to obtain technology and instrumentation development projects that are complementary to the current research program and that support the needs of the other NSBRI research areas. Emphasis in all proposals should be on computer control and automation for ease of operation and speed in conducting the activity. Similarly, all human sample collecting and monitoring should be minimally invasive or non-contact. All projects being developed for ultimate space flight must address size, weight, safety, and other dynamic conditions of space operations. This solicitation will generally focus on projects that deliver a specific product in a specified period of time, typically one to four years. Proposals will be expected to be of a maturity equivalent to that of a typical NASA Phase A (Conceptual Design) study. Proposals should address one of the following needs.

Non-Invasive Physiological Monitoring. Development of instruments or devices to monitor vital signs, core body temperature, eye motion, body fluid chemistry, etc. Sensor and sensor systems for use in long-duration space missions and comparable ground-based research should be easy to use, non-invasive (or minimally invasive), comfortable to wear, unobtrusive, and non-interfering with task performance. Particular emphasis should be placed on flexible and adaptable devices and systems that can be used for multiple purposes and that automatically collect and store data.

Automated Assay and Sample Processing Equipment. Development of automated approaches to carrying out biochemical assays (especially inflight) with minimal operator intervention. Biochemical assays of cellular function require multiple steps in which cells of interest are isolated from other cells, incubated with replacement media, exposed to particular reagents, and then analyzed. There is a generic need for a means of handling samples in which sequential incubations and washes may be performed both on Earth and in space-based environments in an automated manner.

Minimally Invasive Automated Sampling Device. Development of devices to collect blood and other bodily fluids with minimum patient disturbance and discomfort. Frequent measurement of analytes in blood and other serous fluids can indicate the need for or the effectiveness of countermeasures. Long term, a noninvasive body-worn device which can continuously collect and analyze tiny quantities of blood or body fluids would be of extreme

importance. In the shorter term, an easy-to-use, non- or minimally invasive method of withdrawing or collecting such fluids without the problems and discomfort of frequent blood draws would be a major aid to space research.

IV. Application Procedures for the Opportunity to Participate on a National Space Biomedical Research Institute Team

Proposals to join an NSBRI research team must comply with the requirements of this research opportunity as described in this appendix (Appendix C). Appendix E outlines general NASA-specified requirements for proposal submission and should be used only for clarification of matters not specifically discussed here. Appendix C supersedes, modifies or extends the requirements enumerated in Appendix E.

General Instructions

Proposals to join one of the NSBRI's research teams must utilize NSBRI's Internet-based Electronic Proposal Submission System (EPSS). This system has been designed to enable one or more investigators to collaborate on the development of a proposal, to retain complete privacy throughout the proposal development process and to allow fast and accurate proposal submission. If a proposal is selected for funding, the electronic proposal information will serve as an active record file, enabling simplified investigator information changes, annual report submission and NASA Task Book submission.

This electronic submission system automatically prepares and submits a notice of intent to propose. To assure that the notice of intent is submitted by **November 30, 2001**, go to the Web site https://myportal.nsbri.org/myportal.cfm and register to obtain a personal account on the system. After entering contact information, investigators will receive a username and password for entry into EPSS and can enter the limited information required for a notice of intent. After this, the above Web address will serve as the entry point for proposal development and modification. All information entered, with the exception of the information required for the notice of intent, will remain private until electronic submission is completed.

Proposal information requested closely follows the information requested by NIH grant application form PHS 398. This information includes Basic Personal and Institutional Information, Project Description, Performance Sites, Key Personnel, Investigator Budgets with Justifications, Other Support, Biographical Sketches, Laboratory Resources, and Research Plan.

A proposal overview screen will guide applicants through the process of completing the required proposal information. EPSS offers a collaborative work environment for the Principal Investigator and Co-Investigators to view and submit various portions of the proposal. For example, the Principal Investigator can enter or upload <u>all</u> information for the proposal. Co-Investigators can view all proposal information but are permitted to enter only their <u>specific</u> personal information and their assigned project and budgetary information. All investigators can allow an administrative support person to act on their behalf, assisting them in the entry of their proposal information. EPSS will contain an Investigator Profile section, containing biographical sketches and other information, for each investigator registered in the system. This information can be used by authorized proposing investigators, eliminating the duplicate entry of such information.

Electronic applications must be submitted before 5:00 PM, EST, Thursday, January 31, 2002. After submission using EPSS, the Principal Investigator **must** mail a printed proposal cover page, with the appropriate institutional approvals, to the following address within one week of the submission deadline:

Ronald J. White, Ph.D.
Attn: NRA 01-OBPR
NSBRI
One Baylor Plaza, NA-425
Houston, TX 77030-3498
(713-798-7412)

Please direct any questions concerning this application procedure to the NSBRI by calling 713-798-7412, by faxing your questions to 713-798-7413, or by sending your inquiry to contact_us@www.nsbri.org. The technical requirements to operate EPSS are Internet Explorer 4.0+ or Netscape 4.03+ for Windows, Macintosh or Unix. EPSS is best viewed using Internet Explorer 6.0.

Eligibility - Current Principal Investigators funded by the NSBRI are NOT eligible to propose to this NRA. In addition, current Team Leaders and Associate Team Leaders are NOT eligible to serve as Co-Investigators on studies proposed by other Principal Investigators.

Notice of intent – To facilitate planning for the review process, investigators are requested to submit a notice of intent to propose by using EPSS and following the online instructions. This non-binding notification should be completed by November 30, 2001.

Budgetary Matters – Budgets are to be prepared according to the instructions provided online through EPSS. It is expected that the average annual total (direct + indirect) cost of selected proposals will be between $200,000 and $250,000. In general, the annual total cost of a single proposal may not exceed $400,000. ***Investigators should be aware that NSBRI awards require an institutional contribution to the proposed project (cost sharing) at the level of at least 10% of the total NSBRI award. This contribution is not to be identified in the submitted project budget but will be requested at the time the institutional award is made.***

Duration of Proposed Research – Proposals may be submitted for a maximum duration of one to four years funding, with an assumed start date of October 1, 2002. Some applicants may be invited to initiate their project earlier, from July to September 2002.

Special Ground Facilities – A variety of special ground research facilities, including centrifuge facilities, bed rest facilities, etc., are available for use by investigators submitting proposals in response to this NRA. Interested investigators are referred to the *Space Life Sciences Ground Facilities Information Package* for instructions on how to incorporate the use of these facilities into a proposal (see http://research.hq.nasa.gov/code_u/nra/current/NRA-01-OBPR-07/index.html/). The NSBRI will negotiate appropriate use of those facilities on behalf of selected investigators, but investigators must include the cost of using these facilities in their proposal.

Special Travel and Reporting Requirements – Principal Investigators selected in response to this NRA will be expected to attend two, two-day research team meetings each year at a location to

be determined and one, annual, three- to four-day general investigator workshop/retreat in the Houston area. Budgets should reflect the costs associated with these meetings and should include a statement indicating that this travel is a special requirement. Selected investigators will become part of the NSBRI's intramural research program and will be expected to provide an annual progress report. Progress is reviewed by the NSBRI's Board of Scientific Counselors. In addition, investigators will be required to provide annual project information for inclusion in NASA's Life Sciences Program Tasks and Bibliography. The progress report and Task Book information will be collected electronically.

Data Management Plan – Most data collected through NSBRI support are required to be placed in a central Institute data archive. Investigators should plan for delivering their data to the NSBRI archive ***as it is collected*** and should include the cost of such data archiving in their submitted proposal. If selected, a data management plan, including a list of the data products and a schedule for their delivery, must be prepared and submitted to the NSBRI. No additional costs should accompany this plan.

V. Review and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the review and selection process. Elements of review and selection unique to the NSBRI are as follows:

Applications will be evaluated for scientific and technical merit and for the likelihood that the research proposed will have a significant impact on achieving the goals stated in this NRA. The initial review will be carried out by an appropriate panel of experts who will discuss and provide a written critique of each proposal. Proposals deemed to be in the competitive range for this submission will receive a second-level review by the NSBRI scientific program directors to determine relevancy of the proposed project to the research program in the research area under consideration. For studies involving human subjects, adequacy of plans to include both genders and minorities and their subgroups as appropriate for the research goals and plans for subject recruitment and retention will be taken into account. Applicants should be aware that some meritorious proposals may not be selected for funding. Selection recommendations, based on merit score, programmatic relevance, and cost, are prepared by NSBRI management, reviewed by the NSBRI External Advisory Council, and approved by the NSBRI Board of Directors. Final selection will be coordinated between the Bioastronautics Research Division at NASA headquarters and the NSBRI to insure programmatic balance and elimination of duplicate efforts.

Selection will be based on the merit score awarded by the peer review panel, on the programmatic relevance as determined by NSBRI management, and on cost. The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. For studies involving human subjects, adequacy of plans to include both genders and minorities and their subgroups as appropriate for the research goals and plans for subject recruitment and retention will be taken into account.

Original signed by
Bobby R. Alford, M.D.
Chairman of the Board and CEO

Multiple Opportunities for Ground-Based Research in Space Life Sciences
Technical Description

Opportunity to Participate in the Countermeasure Evaluation and Validation Project (CEVP)

I. Introduction

The CEVP provides a mechanism for proposing experiments that, in an integrated fashion, will systematically and scientifically evaluate and validate candidate countermeasures that have reached a high degree of maturity. Such candidate countermeasures will have been experimentally tested in scientific studies designed to test their effects on the target system. That is, they will have completed testing at CRL 6, usually in a ground-based analog of space flight (See Appendix A, III for a discussion of the CRL scale). In the CEVP, they will be evaluated experimentally using ground-based analogs of space flight to assess their targeted effects, their side effects, and their interactions with other countermeasures. After evaluation, a candidate countermeasure may be validated in systematic experiments during actual space flight to assess those same factors. This NRA solicits experiments to test proven countermeasures in bed rest ground studies only (a microgravity analog).

The CEVP functions using a team approach, in which the investigator becomes a member of a team led by the NASA Johnson Space Center (JSC) that integrates space medicine and space research expertise resident inside and outside the agency. The CEVP is the final step in a process in which ideas and concepts emerging from basic research are developed into operational countermeasures and turned over by researchers to be implemented as part of mission operations.

The CEVP uses a baseline standardized complement of integrated physiological and psychological tests, termed the Integrated Testing Regimen (ITR), that will be used to examine candidate CM efficacy and intersystem effects.

II. Focused Investigation Questions and Opportunities Specific to CEVP

The objective of this solicitation is to obtain ground-based, bed rest investigations on human subjects that are complementary to or that enhance the current complement of countermeasures of the CEVP. Competitive proposals submitted in response to this NRA MUST be an evaluation of experimentally proven mature countermeasures that

- **are at the levels of CRL 7 and 8 (see Appendix A, Section III)**. Proposals submitted to CEVP that do not meet the CEVP CRL requirement may be considered under one of the other research opportunities of this solicitation.

- **address two primary risk areas: 1) bone loss and/or 2) muscle loss.** The strategies employed in both these areas must balance the requirements to maintain bone and muscle integrity while minimizing operational costs, such as crew time and extensive hardware development.
- are focused on the use of currently available flight hardware.
- determine contingency capabilities and protocols designed to minimize deconditioning in the event CVIS, TVIS and/or iRED are unavailable. Some examples of current contingency devices are described in section VIII of this appendix.
- use the Integrated Testing Regimen (ITR) as the primary countermeasure evaluation tool.
- consider use of the "small n" statistical tools to minimize the number of subjects (See Reference 24 in Appendix A).

Information about the CEVP is available from

John N. Evanoff, Ph.D.
NASA Johnson Space Center
Human Adaptation & Countermeasures Office
2101 NASA Road 1, Mail Code SK2
Houston, Texas 77058-3696
Telephone: 281-244-6426
Fax: 281-483-2888
Email: jevanoff@ems.jsc.nasa.gov

Collection of Countermeasure-Unique Data

Use of unique tests, essential to the evaluation of the efficacy of a particular proposed countermeasure, may be necessary in addition to the standard ITR tests. These tests, expected to be minimal in number, will be collected on all test subjects and must be well justified by the investigator in the Research Proposal Form. Countermeasure-unique tests will be of lower priority than ITR tests for funding and scheduling. Additional ancillary tests, to be completed as part of the study, but not essential to evaluation of the candidate countermeasure, may be included in the proposal (and costed in the proposal budget). The supplementary tests will be considered as long as they do not confound the primary objective of the study.

Statistical Considerations

Bed rest studies are limited to relatively small subject numbers due to constraints on facilities and funding. Proposals must address statistical considerations and show how the experimental results are generalized. Strategies to limit the requirement for control subjects (e.g., use of "historical" controls from earlier bed rest studies) should be considered in the experimental design. These and other options and their potential benefits should be presented within the proposal.

The National Academy of Science's Institute of Medicine recently completed a review of methodologies for small number clinical trials at the request of NASA. A summary of this meeting and recommendations may be found on the Web site http://www.iom.edu/IOM/IOMHome.nsf/Pages/smalln. The full text of the Institute of Medicine report is available online at http://books.nap.edu/catalog/10078.html.

Current Protocols using Existing Hardware under Nominal Conditions

Proposals should be focused on the use of currently available flight hardware or minor derivatives of such hardware. Such research could compare the efficacy of these modified exercise prescriptions vs. the baseline with the intent of increasing efficacy or minimizing operational consequences of exercise, such as decreasing crew exercise time requirements. Studies requiring exercise in bed rest subjects should specify how the exercises are to be performed in a horizontal position, and any ancillary support equipment that will be required. Studies requiring augmented instrumentation above what is currently available in the flight hardware suite [Interim Resistive Exercise Device (iRED), Treadmill with Vibration Isolation System (TVIS), or Cycle Ergometer Vibration Isolation System (CEVIS)] should clearly specify these capabilities and define concepts and costs for implementation on the ground.

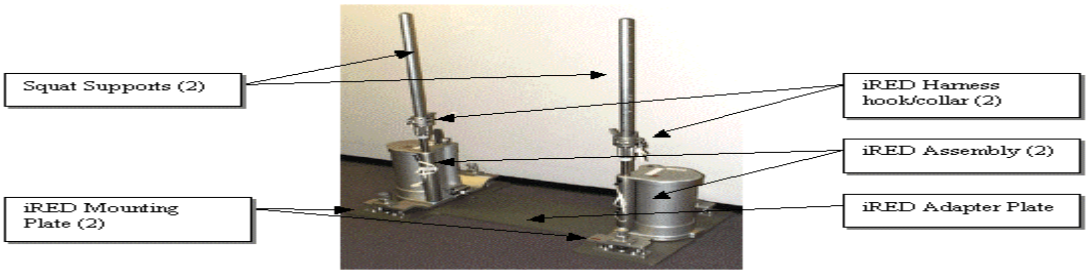
Submitters should take notice that NASA is working in collaboration with the European Space Agency (ESA) on countermeasure evaluation studies being conducted at the Institute for Space Physiology and Medicine (MEDES) facility in Toulouse, France. Both NASA and ESA are using the ITR as a common measure, and studies will be coordinated. For example, one of the countermeasures currently undergoing bed rest evaluation at MEDES is evaluating the efficacy of bisphosphonates as a countermeasure against bone loss. Therefore, studies proposing the use of bisphosphonates will not be considered.

Regular exercise is planned during all ISS operations. Current exercise capabilities are limited to the equipment and protocols defined herein and form the basis of NASA's operational exercise countermeasure program. Exercise prescriptions are tailored to the individual needs of various crewmembers, but all will follow the guidelines defined herein. Nominally, exercise prescriptions are developed based on pre-flight physical fitness testing, and these prescriptions are modified during the mission based on feedback from the crew, operational constraints, or the results of the monthly in-flight Physical Fitness Exam (PFE) conducted on ISS crew. Exercise prescription logs are developed by the NASA-JSC Astronaut Strength, Conditioning, and Rehabilitation (ASCR) group, maintained by the crew, and are downlinked to the ground on a periodic basis.

The following devices and protocols describe the current ISS exercise regimen:

1) **Interim Resistive Exercise Device (iRED)** – The iRED hardware (see Figure 3) provides the ability to perform resistive exercise in a zero gravity environment. The iRED currently resides in the U.S. Node on the ISS. The iRED is comprised of two main canisters, containing rubber "flex packs," which provide a selectable range of resistance from 5 to 150 lbs per canister. The resistance is controlled by rotating a hand crank to preload the flexpacks to the desired resistance, and for loads of 100 pounds or less, adjustability is provided in increments of 5 pounds resistance at an accuracy of ±1 pound or +5% of current reading, whichever is greater. For resistance greater than 100 pounds, adjustability is in increments of 10 pounds resistance at an accuracy of ±1 pound or +5% of current reading, whichever is greater. The canisters may be operated independently or in tandem. A cord exiting the bottom of each canister provides for attachment to a suite of accessories allowing unilateral or bilateral operations, including a deadlift bar, squat harness, ankle cuffs, and handgrips.

Figure 3. Interim Resistive Exercise Device (iRED)



The iRED supports a number of exercises targeting several major muscle groups. Among these are squats, deadlifts, heel raises, knee raises, hip abductions, leg curls, bent-over rows, upright rows, shoulder raises, shoulder presses, bicep curls, tricep extensions, and wrist curls. The iRED provides both concentric and eccentric capability during exercise, with eccentric resistance ranging from 40-60% of the concentric resistance. Due to maximal rotation constraints on the flexpacks, the range-of-motion is limited to 22" for high loads and is progressively higher as loads decrease.

The prescription for iRED exercises varies according to the unique needs and fitness of individual crewmembers, the mission phase, availability of other exercise equipment, and operational and timeline constraints. It is usually updated on a biweekly basis. In general the prescription is written with the intent to alternate lower body and upper body exercises every other day and to minimize the iRED reconfiguration time for the crewmember. Table 1 shows an example of the types of exercise conducted during weekly resistive exercise training program using the iRED. The bottom of the table shows the various phases of training based on mission duration (nominally 4 months).

Table 1. Sample week of inflight iRED exercise

Day 1	**Day 3**	**Day 5**
deadlift	squat	deadlift
bent over rows	heel raises	bent over rows
straight leg deadlift	straight leg deadlift	straight leg deadlift
squat	deadlift	squat
heel raises	bent over rows	heel raises
Day 2	**Day 4**	**Day 6**
shoulder press	bicep curls	shoulder press
rear raises	tricep kickbacks	lateral raises
front raises	upright rows	front raises
hip abduction	hip flexion	hip abduction
hip adduction	hip extension	hip adduction

2 weeks	adaptation	12-15 reps/2-3 sets
4 weeks	basic strength	10-12 reps/2-4 sets
5 weeks	hypertrophy	8-10 reps/2-4 sets
5 weeks	strength	6-8 reps/2-4 sets

2) **Treadmill with Vibration Isolation System (TVIS) –** The TVIS (see Figure 4) is designed to provide treadmill exercise in a microgravity environment while minimizing the structural loads imparted into the ISS structure during exercise. The treadmill is designed to allow walking, running, and knee bends; and provides cardiovascular exercise, ambulation (neuromuscular patterning), axial skeletal loading (heel strike), and endurance exercise of the

anti-gravity musculature. The vibration isolation system is intended to minimize the transfer of dynamic forces caused by operation of the treadmill to the structure of the Service Module (SM) and other parts of the International Space Station (ISS), while at the same time maintaining a stable running/walking surface.

The TVIS is programmable and can be operated in either motorized tread belt or non-motorized (passive) modes. Speed ranges from 0-10 mph in increments of 0.1 mph. In the passive mode, the TVIS uses the motor as a required resistance. The Subject Load Device, a bungee system that attaches to a harness that impacts the downward force on the crewmembers hips and shoulders, accommodates loading. The load can be varied from 40% to 100% total body weight depending on comfort and desired workout. Nominal exercise usually is conducted at the 60-80% load setting. The operator is constrained in the forward/aft direction by use of the Subject Positioning Device, which provides stabilizer bars attached to the TVIS harness and the TVIS platform. A record of the actual exercise speed, load setting, and duration will be recorded onto the PCMCIA card and will nominally be downloaded to the ground for evaluation. If the optional Heart Rate Monitor is worn, heart rate during the exercise will also be recorded.

As in the iRED, individual prescriptions will vary; however, nominal TVIS usage will be planned for a minimum of four sessions per week and will be complemented on alternate days with the Cycle Ergometer Vibration Isolation System (CEVIS - see next section). A typical weekly prescription between the TVIS and CEVIS would be as follows:

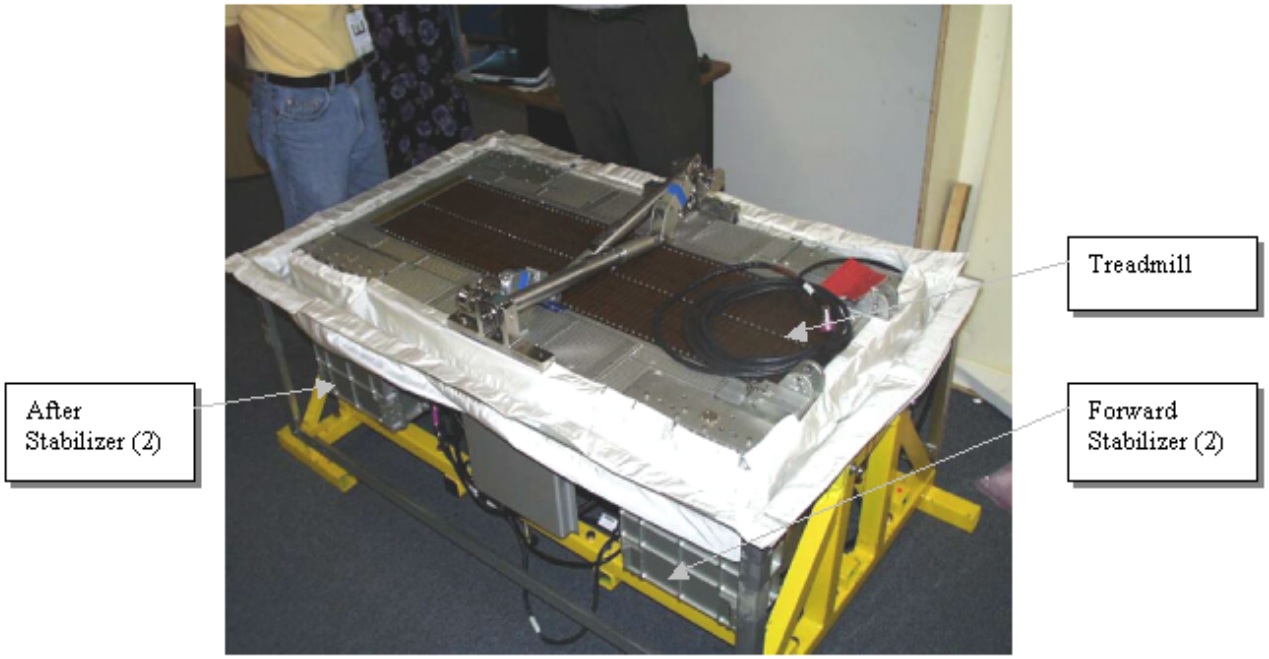
Table 2. Weekly prescription between the TVIS and CEVIS

Day 1	TVIS Interval Training (sprint with walk recovery) (RPMs & length of recovery will vary based upon crewmembers' fitness levels.)
Day 2	CEVIS aerobic training and upper limb resistance training
Day 3	TVIS aerobic training (continuous running) (Time varies based upon crewmembers' fitness levels.)
Day 4	Repeat Day 1
Day 5	Repeat Day 2
Day 6	Repeat Day 3
Day 7	Rest or Interval Training

Individual prescriptions for time and distance exercised will vary depending on preflight and inflight assessments of the crewmember.

Protocols will gain intensity as the mission proceeds. In the final 30 days prior to landing, all aerobic exercise sessions are scheduled on the treadmill (vs. the CEVIS) to promote re-adaptation to earth gravity.

Figure 4. Treadmill with Vibration Isolation System (TVIS)



3) **Cycle Ergometer with Vibration Isolation System (CEVIS)** – The CEVIS (see Figure 5) is located in the U.S. Laboratory Module and provides a variable resistive load for maintaining cardiovascular fitness. The CEVIS can provide independent upper and lower limb cyclic training. The CEVIS is also used for the monthly periodic fitness evaluations. The CEVIS incorporates a resistive mechanism actuated by a manual control as well as a remote electronic controller that provides a workload range from 0 to 350 Watts, described below:

   a) Using the manual controller, the CEVIS workload is continuously variable between 0 and 350 Watts for pedal speeds between 30 and 120 revolutions per minute (rpm). Pedal speeds are adjustable in 5 rpm increments. The workload is displayed during manual control is adjustable in increments of 25 Watts (+/- 5 Watts).

   b) Using the remote electronic controller, the workload may be varied between 25 and 350 Watts, adjustable in discrete units of 1 watt, for pedal speeds between 50 to 120 rpm (+/- 1 rpm).

The nominal prescription for CEVIS is shown in Table 2. A record of the load, speed, and duration is recorded onto the PCMCIA card and downloaded to the ground for evaluation. If the optional Heart Rate Monitor is worn, heart rate during the exercise will also be recorded.

Figure 5. Cycle Ergometer with Vibration Isolation System (CEVIS)

Current contingency exercise capability on ISS

In the event that the nominal ISS exercise equipment (TVIS, CEVIS, or iRED) fails, NASA must develop and maintain contingency capabilities and protocols designed to minimize deconditioning experienced while awaiting repairs. To date, the following contingency capabilities exist:

- TVIS failures – there are a number of potential failures for TVIS that would degrade TVIS performance. Possible failures include the active motor, Subject Load Device, or the tread. Failure of the motor would require "passive" operation, where the operator drives the tread. Failure of the Subject Load Device would necessitate a contingency loading mechanism, such as bungee cords attached to the TVIS harness and 4-point attachment to the TVIS structure. Complete failure of the TVIS would require an alternate running surface, such as the Contingency Exercise Surface (CES). The CES is a Teflon-coated aluminum plate that mounts over the TVIS tread. The user dons slippery booties over their shoes, and then uses the same accessories as the TVIS for loading and positioning (SLD and the user can "moonwalk" across the near frictionless surface, emulating a running motion to the maximum extent possible).

- IRED failures – the iRED has multiple failure modes, which also degrade performance. In the event of failure of one or both of the iRED canisters, the Contingency Resistive Exercise System (CRES) can be used to provide resistive loading. The CRES is comprised of four sets of bungee cords. Each set is comprised of a pair of bungees, with each bungee rated up to 100 lbs at full 36-inch extension; however, at the usual extension (~ 22 inches) for squats, a resistance of 60 lbs is more typical (therefore, squats with four sets of bungees would net 480 lbs resistance at maximum range of motion). The CRES bungees can be installed individually or in pairs to the iRED footplate and attachments.

Note that CEVP proposals will be evaluated for their responsiveness to the critical needs expressed in this NRA. Proposals that are not responsive to these needs will not be selected for funding.

III. Integrated Testing Regimen

A standardized set of operational, medical, physiological and psychological tests have been adapted by the CEVP for obtaining systematic measurements before, during, and after space flight. This complement of tests is called the Integrated Testing Regimen (ITR). The ITR will be used to examine the efficacy of candidate countermeasures on the target physiological system(s) as well as to evaluate the side effects and/or interactions of the countermeasures on non-target systems.

Discipline-specific Integrated Product Teams comprised of flight surgeons, space research experts, and operations experts will establish success/criteria criteria for physiological performance measures in each of the target disciplines and will review/update these criteria on a regular basis. Creation of predetermined, objective ratings of success and failure will facilitate statistical analysis of a countermeasure's efficacy. Success/failure criteria address functional and clinical capabilities projected during long-duration space flight and must be evaluated from test data derived from the CEVP ITR. Given the importance of countermeasure development and validation to the OBPR objectives, all crewmembers on every long-duration ISS mission will be requested to participate in either the ITR alone, or the ITR as part of countermeasure validation. **Ground-based ITR testing in conjunction with this solicited bed rest study will be required.**

Table 3. Integrated Testing Regimen (ITR) – Primary Evaluation Tool

Test	Description	Test Performed in Relation to Bed Rest
Operational Tilt Test	Subject will be tested on the tilt table in supine and standing positions. Measurements of blood pressure, heart rate, stroke volume, cardiac output and peripheral resistance are collected.	*(pre - post)*
Clinical Lab Assessment (fasting)	Blood and urine are collected for analysis.	*(pre - post)*
Clinical Nutritional Assessment	A diet questionnaire is filled out, and height and weight are taken pre-, in-, and post bed rest. Blood, urine and saliva are collected pre and post bed rest, as well as bone densitometry (DEXA) data.	*(pre - post)*
Bone Densitometry	5 DEXA scans are taken: heel, hip, wrist, whole body and lumbar spine.	*(pre - post)*
Functional Neurological Assessment	Subject is placed on the posture platform where tests for balance control and sensory integration are administered.	*(pre - post)*
Functional Fitness	Exercises used for testing are bench press, crunches, leg press, sit & reach, push-ups, and pull-ups.	*(pre - post)*
Isokinetic Muscle Function	Muscle performance testing will be administered using an isokinetic dynamometer on back extensors/abdominal, hamstring/quadricep and tibialis anterior/gastro-soleus groups.	*(pre - post)*
Test of Aerobic Capacity: Cycle Ergometry	A maximal and submaximal upright cycle test will be administered. The max test will establish a max heart rate and V02. The submax test will establish the protocol for in-flight exercise.	*(pre - in - post)*
Neurocognitive Assessment	A computer-based test is administered on the Medical Equipment Computer.	*(pre - in - post)*

IV. Ground Analog Campaign Description

Research selected through this NRA will be managed under NASA's CEVP, an element of the NASA Biomedical Research and Countermeasures Program. Under the CEVP, NASA will provide and support a space flight analog bed rest study for the evaluation of countermeasures targeting bone and muscle loss. Research that proposes bed rest facilities outside of the CEVP facility will not be considered.

The CEVP solicits proposals to evaluate mature candidate countermeasures for testing in a bed rest study. Dependent measures for these studies are defined by the Integrated Testing Regimen (ITR). **Due to the high cost of conducting bed rest studies, proposals selected through this CEVP NRA may be "teamed" and coordination of the protocols will be performed by CEVP and the selected investigators. The bed rest study will be performed at a facility designated by the CEVP, and all subjects participating in countermeasure evaluation studies will be tested using a ground-based version of the ITR.**

CEVP Database for Ground Evaluation Studies

CEVP ITR ground data will be archived in a dedicated CEVP database maintained within the Life Sciences Data Archive infrastructure at JSC. NASA CEVP Project Management will strictly control access to test subject data. Data requests for CEVP ground data will be screened through and approved by a CEVP Review Committee and management configuration control board. Test subjects will be briefed prior to enrolling in the bed rest campaign, and must sign an Informed Consent Form allowing sharing of data with CEVP investigators prior to study enrollment.

Data collected for the CEVP will be coded to assure test subject confidentiality. Protection will include use of unique codes assigned to each test subject on all paper, electronic, audio, and videotape data records. Published results may not identify or be able to identify any test subject unless consent to do so is specifically granted by the test subject.

V. Funding

Since NASA will provide and support the space flight analog infrastructure, including test subjects, supplies, sample analysis, and the ITR, it is anticipated that the proposing PI costs are to be minimal. **It is expected that a typical ground proposal award will average $120,000 (total annual costs). It is anticipated that only two to four ground-based CEVP proposals will be funded by this Research Opportunity due to facility and funding limitations for bed rest studies**. **Because of this limitation, investigators should very carefully review the focus of this section of the solicitation identified in Section II "Focused Investigation Questions and Opportunities Specific to CEVP."**

VI. Facilities

Sites that may be used by CEVP for ground-based countermeasure evaluations include the NASA Ames Research Center Human Research Facility and/or other facilities local to the NASA Johnson Space Center (JSC). These facilities will provide a core staff of nurses, medical monitoring personnel, technicians, and dieticians to provide a turn-key, end-to-end capability for conducting countermeasure evaluation studies using long-duration bed rest as a space flight analog. In addition, facility personnel will perform the ITR (see Figure 1) on all bed rest subjects.

VII. Test Duration

Current anticipated dates for the bed rest studies solicited by this NRA will be of 30-90 days in duration and will be performed in the January – March 2003 and/or June - August 2003 timeframe.

VIII. Application Procedures for Individual Investigations Proposing to the Countermeasure Evaluation and Validation Project

Instructions for Notice of Intent and Proposal Submission

Proposals for individual investigator grants must comply with the general requirements of this research opportunity as described in this appendix (Appendix D). Appendix E outlines general NASA specified requirements for proposal submission, and should be used for clarification and reference. This appendix supersedes, modifies, or extends the requirements enumerated in Appendix E.

SYS-EYFUS Registration for All Applicants

SYS-EYFUS is an electronic system used by NASA Headquarters to manage research solicitation activity, plan for the receipt of research proposals, track the receipt and peer evaluation of these proposals, and manage funded research (grants, cooperative agreements, etc.) sponsored by NASA's Office of Equal Opportunity (Code E), Office of Earth Science (Code Y), Office of Human Resources & Education Division (Code F), Office of Biological and Physical Research (Code U), Office of Space Science (Code S), and the Office of Space Flight (Code M). SYS-EYFUS also supports the funding and administration of awards pursuant to selection of these research opportunities.

All investigators planning to submit a proposal to this solicitation are requested to register online with SYS-EYFUS. Comprehensive help, instructions, and contact information are provided online. SYS-EYFUS can be accessed at the following address:

http://proposals.hq.nasa.gov/

If you have previously registered with SYS-EYFUS, you are requested to verify and update your user information. If you have forgotten your user ID or password, select the "Forgot Your Password" option and type in your first and last name to search our database. The system will

send an automatic email message with your username and password to the email address listed in our database.

Instructions for Preparing a Notice of Intent

All investigators planning to submit a proposal in response to this solicitation are requested to submit a **non-binding** Notice of Intent (NOI) to propose by November 30, 2001, via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS and select "New Notice of Intent."
- The Division Specific Opportunities screen will appear. In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Notice of Intent submission Form. All fields are required.
  a. For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002.
- Click on "Submit NOI Page."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the NOI. After you are done, click on "Continue." IMPORTANT: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Members Page, your NOI will be displayed. Click on "Resubmit NOI Page" to complete your NOI submission.
- You may edit and resubmit your NOI at any time before the submission deadline of November 30, 2001. Once you submit an NOI, it cannot be deleted. For title, team member, or any other changes, please edit your existing NOI and resubmit changes to avoid duplicate records.

Instructions for the Preparation of Proposals

An original signed proposal, plus twenty (20) complete copies of the proposal, should be mailed to the address indicated and in the manner described of this document.

All proposals submitted to the Bioastronautics' Biomedical Research and Countermeasures Program must include the completed cover page form as described in this Appendix. The name of the Principal Investigator should appear in the upper right hand corner of each page of the proposal, except on the cover page form where special places are provided for this information. Note that the proposal must specify the period of performance for the work described; periods of

performance may be for any duration up to three (3) years but should be suitable for the project proposed.

The proposal must include the following material, in this order:

(1) Proposal Cover Page: Solicited Proposal Application, including certification of compliance with U.S. code (if applicable). One signed original required. Please see "How to Submit Proposal Cover Page Information" below for instructions on how to complete the proposal cover page information.

(2) Transmittal Letter or Prefatory Material, if any (see Appendix E for details)

(3) Proposal Title Page, with Notice on Restriction on Use and Disclosure of Proposal Information, if any (see Appendix E for details)

(4) Project Description

The length of the Project Description section of the proposal cannot exceed 20 pages using regular (12 point) type. Referenced figures must be included in the 20 pages of the Project Description. The Bibliography section is not considered part of the 20-page project description. Proposals that exceed the 20-page limit for the project description (22-page limit for revised proposals; see below) will not be reviewed. The proposal should contain sufficient detail to enable reviewers to make informed judgments about the overall merit of the proposed research and about the probability that the investigators will be able to accomplish their stated objectives with current resources and the resources requested. In addition, the proposal should clearly indicate the relationship between the proposed work and the research emphases defined in this Announcement. Reviewers are not required to consider information presented as appendices or to view and/or consider Web links in their evaluation of the proposal.

New applications, where the investigator has received NASA funding in related fields from 1999 through 2001, must present results and evidence of progress of the associated NASA-supported research as part of the project description.

Revised applications (revisions of 1999, 2000 or 2001 submissions) must be so designated on the proposal cover page and explained in the project description. This explanation should be presented in a separate section of **no more that two pages at the beginning of the project description**, and is in addition to the 20 pages allowed for the project description. Related changes to the research plan should be highlighted in the body of the project description. Changes within the proposal may be highlighted by appropriate bracketing, indenting, or changing of typography. Clearly present any work done since the prior version was submitted. **Revised applications that do not address the criticisms in the previous review will be considered unresponsive and will be returned without review.**

(5) Management Approach

Each proposal must specify a single Principal Investigator who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. In proposals that designate several senior professionals as key participants in the research project, the management approach section should define the roles and responsibilities of each participant

and note the proportion of each individual's time to be devoted to the proposed research activity. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation.

(6) Personnel / Biographical Sketches

The biographical sketch for each investigator should not exceed two pages. If the list of qualifications and publications exceeds two pages, select the most pertinent information (see Appendix E for details).

(7) Other Support (see Appendix E for details)

(8) Facilities and Equipment (see Appendix E for details)

(9) Special Matters (specific information on animal or human subjects protocol approval required, if applicable)

The Special Matters section must contain a statement from the investigator's institution that states that the proposed work will meet all Federal and local human subject requirements and animal care and use requirements, if applicable. Note that no animal subjects may be utilized unless specific information justifying and describing their use is included in the proposal. Policies regarding the protection of human research subjects in NASA-sponsored research are detailed in NASA Management Instruction (NMI) 7100.8B (Protection of Human Research Subjects), and animal care and use requirements are detailed in the NASA Code of Federal Regulations (CFR) 1232 (Care and Use of Animals in the Conduct of NASA Activities), both of which are available from the Office of Biological and Physical Research, Code UB, NASA Headquarters, Washington, DC 20546. Assurance of compliance with human subject or animal care provisions is required on Form A, to be submitted with each proposal. In addition, a letter signed by the chairperson of the Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC), or both, as appropriate, regarding approval of the experimental protocol, should be included with each copy of the proposal. If IRB or IACUC review is unavoidably delayed beyond the submission of the application, enter "Pending" on Line 9b or 10a of Form A, and be advised that the certification must be received within 60 days after the due date for which the application is submitted. If certification is not received within 60 days after the application due date, the application will be considered incomplete, and will not be reviewed. NASA shall require current IRB or IACUC certification prior to each year's award. All U.S., non-NASA proposals providing IACUC approval must also contain the institution's Public Health Assurance number.

(10) Detailed Budget

NASA is expected to be operating on the basis of full cost accounting as soon as possible, including all Civil Service salaries with overhead. In the interim period, proposals should use the accounting method authorized at their institutions at the time proposals are due and for the entire proposed period of performance. Funds to support the Resident Research Assistant (RRA) Postdoctoral Program costs (e.g., stipend, travel, computer time, supplies, etc.) are to be budgeted within the NASA intramural Principal Investigator budget.

The budget must include travel funds for the Principal Investigator to attend a biannual BR&C Principal Investigator meeting. If other travel is planned, the proposal budget should include appropriate travel funds for visits to NASA field centers (as appropriate) and presentation of findings at professional society meetings.

(11) Supporting Budgetary Information

In this solicitation, the terms "cost" and "budget" are used synonymously. Sufficient proposal cost detail and supporting information are required; funding amounts proposed with no explanation (e.g., Equipment: $1,000, or Labor: $6,000) may cause delays in evaluation and award. Generally, costs will be evaluated for realism, reasonableness, allowability, and allocation. The budgetary forms define the desired detail, but each category should be explained in this section. Offerors should exercise prudent judgment in determining what to include in the proposal, as the amount of detail necessarily varies with the complexity of the proposal.

The following examples indicate the suggested method of preparing a cost breakdown:

Direct Labor
Labor costs should be segregated by titles or disciplines with estimated hours and rates for each. Estimates should include a basis of estimate, such as currently paid rates or outstanding offers to prospective employees. This format allows the Government to assess cost reasonableness by various means including comparison to similar skills at other organizations.

Other Direct Costs
Please detail, explain, and substantiate other significant cost categories as described below:

Subcontracts: Describe the work to be contracted, estimated amount, recipient (if known), and the reason for subcontracting.
Consultants: Identify consultants to be used, why they are necessary, the time they will spend on the project, and the rates of pay (not to exceed the equivalent of the daily rate for Level IV of the Executive Schedule, exclusive of expenses and indirect costs).
Equipment: List separately. Explain the need for items costing more than $5,000. Describe basis for estimated cost. General purpose equipment is not allowable as a direct cost unless specifically approved by the NASA Grant Officer. Any equipment purchase requested as a direct charge must include the equipment description, how it will be used in the conduct of the basic research proposed, and why it cannot be purchased with indirect funds.
Supplies: Provide general categories of needed supplies, the method of acquisition, and estimated cost.
Travel: Describe the purpose of the proposed travel in relation to the grant and provide the basis of estimate, including information on destination and number of travelers (if known).
Other: Enter the total of direct costs not covered previously. Attach an itemized list explaining the need for each item and the basis for the estimate.

Indirect Costs
Indirect costs should be explained to an extent that will allow the Government to understand the basis for the estimate. Examples of prior year historical rates, current variances from those rates, or an explanation of other basis of estimates should be included. Where costs are based on allocation percentages or dollar rates, an explanation of rate and application base relationships

should be given. For example, the base to which the General and Administrative (G&A) rate is applied could be explained as: application base equals total costs before G&A less subcontracts.

All awards made as a result of this NRA will be funded as grants. However, while proposals submitted by "for profit" organizations are allowed, they cannot include a "fee."

(12) Appendices, if any (reviewers are not required to consider information presented in appendices)

How to Submit Proposal Cover Page Information:

All investigators planning to submit a proposal in response to this solicitation must electronically submit proposal cover page information online and provide a hard copy of the cover page attached to each proposal copy by January 31, 2002. The proposal cover page can be submitted and printed via the Web at the following address:

http://proposals.hq.nasa.gov/proposal.cfm

- Login to SYS-EYFUS.
- To submit a New Proposal Cover Page, click the "New Proposal Cover Page" option from the SYS-EYFUS Options screen, and the New Proposals Cover Page screen will appear.
- If you previously submitted an NOI in response to this solicitation, choose to carry over the existing NOI. This option will populate the cover page fields with the NOI information. Edit the information as necessary, click "Continue" and proceed to the instructions for the Proposal Cover Sheet Submission Form below.
- If you did not previously submit an NOI, click on New Proposal Cover Page option, and the Division Specific Opportunities screen will appear.
- In the selection window, highlight Bioastronautics Research Division and click on "Continue."
- The List of Existing Opportunities screen will appear. In the selection window, highlight 01-OBPR-07 and then click on "Continue."
- This will bring you to the Proposal Cover Page Submission Form. Fill in all the fields. All fields are required.
  For the proposal type field on this form, new/no prior support means that the investigator has not received NASA funding from 1999 through 2001, new/prior support means that the investigator has received NASA funding between 1999 and 2001, and revised means that the proposal is a revised version of a proposal submitted to NASA and reviewed from 1999 through 2001, but not funded. A proposal previously submitted but not funded, should be identified as being "revised" even if the original Principal Investigator has changed for 2002. Click on "Continue."
- The Team Member Page screen will appear, where you can add or remove team members. Select continue if there are no other team members. To add a team member, highlight the role option on the selection list, type in first and last name and click on search. When the resulting set appears, choose the appropriate radio button and click on ADD to add the person to the proposal. After you are done, click on "Continue." **IMPORTANT**: If the team member is not listed in our database, please have them add themselves as a new user to the system. You may then add them to your team member list.
- After continuing from the Team Member Page, the Proposal Options Page appears.

- Please fill out the budget form by clicking on the "Budget" button, filling in project costs, and clicking "Continue." This will bring you to the Proposal Budget Review Page. Click "Continue" if the information is correct.
- After verifying your budget information, you will be returned to the Proposal Options Page. Click the "Show/Print" button.
- At the Page entitled Proposal Information Item List click "Continue" to preview your Proposal Cover Page. Print the cover page from your Internet browser once you have reviewed the information. The cover page must be signed by both the Principal Investigator and the authorizing official and attached to the font of your proposal before submission of hard copies to NASA.
- You may edit and resubmit your proposal cover page at any time before the submission deadline of January 31, 2002. Please note that once you submit a proposal cover page, it cannot be deleted. For title, team member, budget or any other changes, please edit your existing proposal cover page and resubmit changes to avoid duplicate records.
- One (1) signed original and twenty (20) copies of the proposal must be received by 5:00 PM on January 31, 2002, at the following address:

  NASA Peer Review Services
  Subject: 01-OBPR-07
  500 E Street SW, Suite 200
  Washington, DC 20024

CEVP proposals submitted by investigators from the International Space Life Sciences Working Group Agencies' (ISLSWG) members and approved for funding by the ISLSWG member agencies will be reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Any proposals from non-U.S. entity must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

IX. Evaluation and Selection Process

Investigators should refer to Appendix A, Section IV, for a description of the review and selection process. Elements of review and selection unique to the CEVP are as follows:

Upon receipt, proposals will be reviewed for compliance with the requirements of this NRA.

Information resulting from the four levels of review noted below will, in turn, be used for making a selection recommendation by CEVP Science Managers for each of the program elements described in this NRA. This recommendation will be based on

1. Operational Relevance/Feasibility of Implementation
2. Countermeasure maturity/Scientific pedigree
3. Scientific or technical merit review score from the peer review panel

4. Programmatic cost of each proposal

The most important element in the evaluation process is the merit review, which carries the highest weight in final evaluation and selection. The other factors are approximately equal in weight to each other. Funding determination will be made by the Director of the Bioastronautics Research Division at NASA Headquarters for those proposals recommended by the CEVP Science Managers.

APPENDIX E
NRA 01-OBPR-07

Instructions for Responding to NASA Research NRAs
NFS 1852.235-72

(a) General.

(1) Proposals received in response to a NASA Research Announcement (NRA) will be used only for evaluation purposes. NASA does not allow a proposal, the contents of which are not available without restriction from another source, or any unique ideas submitted in response to an NRA to be used as the basis of a solicitation or in negotiation with other organizations, nor is a pre-award synopsis published or individual proposals.

(2) A solicited proposal that results in a NASA award becomes part of the record of that transaction and may be available to the public on specific request; however, information or material that NASA and the awardee mutually agree to be of a privileged nature will be held in confidence to the extent permitted by law, including the Freedom of Information Act

(3) NRAs contain programmatic information and certain requirements which apply only to proposals prepared in response to that particular announcement. These instructions contain the general proposal preparation information which applies to responses to all NRAs.

(4) A contract, grant, cooperative agreement, or other agreement may be used to accomplish an effort funded in response to an NRA. NASA will determine the appropriate instrument. Contracts resulting from NRAs are subject to the Federal Acquisition Regulation and the NASA FAR Supplement. Any resultant grants or cooperative agreements will be awarded and administered in accordance with the NASA Grant and Cooperative Agreement Handbook (NPG 5800.1).

(5) NASA does not have mandatory forms or formats for responses to NRAs; however, it is requested that proposals conform to the guidelines in these instructions. NASA may accept proposals without discussion; hence, proposals should initially be as complete as possible and be submitted on the proposers' most favorable terms.

(6) To be considered for award, a submission must, at a minimum, present a specific project within the areas delineated by the NRA; contain sufficient technical and cost information to permit a meaningful evaluation; be signed by an official authorized to legally bind the submitting organization; not merely offer to perform standard services or to just provide computer facilities or services; and not significantly duplicate a more specific current or pending NASA solicitation.

(b) NRA-Specific Items. Several proposal submission items appear in the NRA itself: the unique NRA identifier; when to submit proposals; where to send proposals; number of copies required; and sources for more information. Items included in these instructions may be supplemented by the NRA.

(c) The following information is needed to permit consideration in an objective manner. NRAs will generally specify topics for which additional information or greater detail is desirable. Each proposal copy shall contain all submitted material, including a copy of the transmittal letter if it contains substantive information.

(1) Transmittal Letter or Prefatory Material.

(i) The legal name and address of the organization and specific division or campus identification if part of a larger organization;

(ii) A brief, scientifically valid project title intelligible to a scientifically literate reader and suitable for use in the public press;

(iii) Type of organization: e.g., profit, nonprofit, educational, small business, minority, women-owned, etc.;

(iv) Name and telephone number of the principal investigator and business personnel who may be contacted during evaluation or negotiation;
(v) Identification of other organizations that are currently evaluating a proposal for the same efforts;
(vi) Identification of the NRA, by number and title, to which the proposal is responding;
(vii) Dollar amount requested, desired starting date, and duration of project;
(viii) Date of submission; and
(ix) Signature of a responsible official or authorized representative of the organization, or any other person authorized to legally bind the organization (unless the signature appears on the proposal itself).

(2) Restriction on Use and Disclosure of Proposal Information. Information contained in proposals is used for evaluation purposes only. Offerors or quoters should, in order to maximize protection of trade secrets or other information that is confidential or privileged, place the following notice on the title page of the proposal and specify the information subject to the notice by inserting an appropriate identification in the notice. In any event, information contained in proposals will be protected to the extent permitted by law, but NASA assumes no liability for use and disclosure of information not made subject to the notice.

Notice: Restriction on Use and Disclosure of Proposal Information

The information (data) contained in [insert page numbers or other identification] of this proposal constitutes a trade secret and/or information that is commercial or financial and confidential or privileged. It is furnished to the Government in confidence with the understanding that it will not, without permission of the offeror, be used or disclosed other than for evaluation purposes; provided, however, that in the event a contract (or other agreement) is awarded on the basis of this proposal the Government shall have the right to use and disclose this information (data) to the extent provided in the contract (or other agreement). This restriction does not limit the Government's right to use or disclose this information (data) if obtained from another source without restriction.

(3) Abstract. Include a concise (200-300 word if not otherwise specified in the NRA) abstract describing the objective and the method of approach.
(4) Project Description.
(i) The main body of the proposal shall be a detailed statement of the work to be undertaken and should include objectives and expected significance; relation to the present state of knowledge; and relation to previous work done on the project and to related work in progress elsewhere. The statement should outline the plan of work, including the broad design of experiments to be undertaken and a description of experimental methods and procedures. The project description should address the evaluation factors in these instructions and any specific factors in the NRA. Any substantial collaboration with individuals not referred to in the budget or use of consultants should be described. Subcontracting significant portions of a research project is discouraged.
(ii) When it is expected that the effort will require more than one year, the proposal should cover the complete project to the extent that it can be reasonably anticipated. Principal emphasis should be on the first year of work, and the description should distinguish clearly between the first year's work and work planned for subsequent years.
(5) Management Approach. For large or complex efforts involving interactions among numerous individuals or other organizations, plans for distribution of responsibilities and arrangements for ensuring a coordinated effort should be described.
(6) Personnel. The principal investigator is responsible for supervision of the work and participates in the conduct of the research regardless of whether or not compensated under the award. A short biographical sketch of the principal investigator, a list of principal publications and any exceptional qualifications should be included. Omit social security number and other personal items which do not merit consideration in evaluation of the proposal. Give similar biographical information on other senior professional personnel who will be directly associated with the project. Give the names and titles of any other scientists and technical personnel associated substantially with the project in an advisory capacity. Universities should list the approximate number of students or other assistants, together with

information as to their level of academic attainment. Any special industry-university cooperative arrangements should be described.

(7) Facilities and Equipment.

(i) Describe available facilities and major items of equipment especially adapted or suited to the proposed project, and any additional major equipment that will be required. Identify any Government-owned facilities, industrial plant equipment, or special tooling that are proposed for use. Include evidence of its availability and the cognizant Government points of contact.

(ii) Before requesting a major item of capital equipment, the proposer should determine if sharing or loan of equipment already within the organization is a feasible alternative. Where such arrangements cannot be made, the proposal should so state. The need for items that typically can be used for research and non-research purposes should be explained.

(8) Proposed Costs (U.S. Proposals Only).

(i) Proposals should contain cost and technical parts in one volume: do not use separate "confidential" salary pages. As applicable, include separate cost estimates for salaries and wages; fringe benefits; equipment; expendable materials and supplies; services; domestic and foreign travel; ADP expenses; publication or page charges; consultants; subcontracts; other miscellaneous identifiable direct costs; and indirect costs. List salaries and wages in appropriate organizational categories (e.g., principal investigator, other scientific and engineering professionals, graduate students, research assistants, and technicians and other non-professional personnel). Estimate all staffing data in terms of staff-months or fractions of full-time.

(ii) Explanatory notes should accompany the cost proposal to provide identification and estimated cost of major capital equipment items to be acquired; purpose and estimated number and lengths of trips planned; basis for indirect cost computation (including date of most recent negotiation and cognizant agency); and clarification of other items in the cost proposal that are not self-evident. List estimated expenses as yearly requirements by major work phases.

(iii) Allowable costs are governed by FAR Part 31 and the NASA FAR Supplement Part 1831 (and OMB Circulars A-21 for educational institutions and A-122 for nonprofit organizations).

(iv) Use of NASA funds--NASA funding may not be used for foreign research efforts at any level, whether as a collaborator or a subcontract. The direct purchase of supplies and/or services, which do not constitute research, from non-U.S. sources by U.S. award recipients is permitted. Additionally, in accordance with the National Space Transportation Policy, use of a non-U.S. manufactured launch vehicle is permitted only on a no-exchange-of-funds basis.

(9) Security. Proposals should not contain security-classified material. If the research requires access to or may generate security-classified information, the submitter will be required to comply with Government security regulations.

(10) Current Support. For other current projects being conducted by the principal investigator, provide title of project, sponsoring agency, and ending date.

(11) Special Matters.

(i) Include any required statements of environmental impact of the research, human subject or animal care provisions, conflict of interest, or on such other topics as may be required by the nature of the effort and current statutes, executive orders, or other current Government-wide guidelines.

(ii) Proposers should include a brief description of the organization, its facilities, and previous work experience in the field of the proposal. Identify the cognizant Government audit agency, inspection agency, and administrative contracting officer, when applicable.

(d) Renewal Proposals.

(1) Renewal proposals for existing awards will be considered in the same manner as proposals for new endeavors. A renewal proposal should not repeat all of the information that was in the original proposal. The renewal proposal should refer to its predecessor, update the parts that are no longer current,

and indicate what elements of the research are expected to be covered during the period for which support is desired. A description of any significant findings since the most recent progress report should be included. The renewal proposal should treat, in reasonable detail, the plans for the next period, contain a cost estimate, and otherwise adhere to these instructions.

(2) NASA may renew an effort either through amendment of an existing contract or by a new award.

(e) Length. Unless otherwise specified in the NRA, effort should be made to keep proposals as brief as possible, concentrating on substantive material. Few proposals need exceed 15-20 pages. Necessary detailed information, such as reprints, should be included as attachments. A complete set of attachments is necessary for each copy of the proposal. As proposals are not returned, avoid use of "one-of-a-kind" attachments.

(f) Joint Proposals.

(1) Where multiple organizations are involved, the proposal may be submitted by only one of them. It should clearly describe the role to be played by the other organizations and indicate the legal and managerial arrangements contemplated. In other instances, simultaneous submission of related proposals from each organization might be appropriate, in which case parallel awards would be made.

(2) Where a project of a cooperative nature with NASA is contemplated, describe the contributions expected from any participating NASA investigator and agency facilities or equipment which may be required. The proposal must be confined only to that which the proposing organization can commit itself. "Joint" proposals which specify the internal arrangements NASA will actually make are not acceptable as a means of establishing an agency commitment.

(g) Late Proposals. Proposals or proposal modifications received after the latest date specified for receipt may be considered if a significant reduction in cost to the Government is probable or if there are significant technical advantages, as compared with proposals previously received.

(h) Withdrawal. Proposals may be withdrawn by the proposer at any time before award. Offerors are requested to notify NASA if the proposal is funded by another organization or of other changed circumstances which dictate termination of evaluation.

(i) Evaluation Factors.

(1) Unless otherwise specified in the NRA, the principal elements (of approximately equal weight) considered in evaluating a proposal are its relevance to NASA's objectives, intrinsic merit, and cost.

(2) Evaluation of a proposal's relevance to NASA's objectives includes the consideration of the potential contribution of the effort to NASA's mission.

(3) Evaluation of its intrinsic merit includes the consideration of the following factors of equal importance:

(i) Overall scientific or technical merit of the proposal or unique and innovative methods, approaches, or concepts demonstrated by the proposal.

(ii) Offeror's capabilities, related experience, facilities, techniques, or unique combinations of these which are integral factors for achieving the proposal objectives.

(iii) The qualifications, capabilities, and experience of the proposed principal investigator, team leader, or key personnel critical in achieving the proposal objectives.

(iv) Overall standing among similar proposals and/or evaluation against the state-of-the-art.

(4) Evaluation of the cost of a proposed effort may include the realism and reasonableness of the proposed cost and available funds.

(j) Evaluation Techniques. Selection decisions will be made following peer and/or scientific review of the proposals. Several evaluation techniques are regularly used within NASA. In all cases, proposals are subject to scientific review by discipline specialists in the area of the proposal. Some proposals are reviewed entirely in-house; others are evaluated by a combination of in-house and selected external reviewers; while yet others are subject to the full external peer review technique (with due regard for conflict-of-interest and protection of proposal information), such as by mail or through assembled panels. The final decisions are made by a NASA selecting official. A proposal which is scientifically and programmatically meritorious, but not selected for award during its initial review, may be included in subsequent reviews unless the proposer requests otherwise.

(k) Selection for Award.

(1) When a proposal is not selected for award, the proposer will be notified. NASA will explain generally why the proposal was not selected. Proposers desiring additional information may contact the selecting official who will arrange a debriefing.

(2) When a proposal is selected for award, negotiation and award will be handled by the procurement office in the funding installation. The proposal is used as the basis for negotiation. The contracting officer may request certain business data and may forward a model award instrument and other information pertinent to negotiation.

(l) Additional Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

Only ground-based proposals submitted in response to this NRA from U.S. entities, or from non-U.S. entities that involve substantive co-investigator collaboration from a U.S. entity, will be reviewed. U.S. co-investigators who are collaborating on such proposals with non-U.S. entities must ensure that their scientific role is clearly delineated in the proposal, that their expertise is shown to make a substantial contribution, and that their funding requirements are included in the proposal. Proposals from non-U.S. entities with significant co-investigator collaboration from a U.S. entity must be endorsed by the respective government agency or funding/sponsoring institution in that country from which the non-U.S. participant is proposing. Such endorsement should indicate that the proposal merits careful consideration by NASA, and if the proposal is selected, sufficient funds will be made available to undertake the activity as proposed. This Letter of Endorsement from the sponsoring non-U.S. government agency or funding/sponsoring institution should be forwarded along with the proposal.

All proposals from non-U.S. entities which involve substantive co-investigator collaboration from a U.S. entity must be typewritten in English and comply with all other submission requirements stated in this NRA. These proposals will undergo the same evaluation and selection process as those originating in the U.S. All proposals must be received before the established closing date. Sponsoring foreign government agencies or funding institutions for proposals from non-U.S. entities meeting the above guidelines may, in exceptional situations, forward a proposal without endorsement to the above address if endorsement is not possible before the announced closing date. In such cases, the NASA sponsoring office should be advised when a decision on endorsement can be expected.

Successful and unsuccessful non-U.S. proposers will be contacted directly by the NASA sponsoring office. Copies of these letters will be sent to the sponsoring government agency or funding institution. Should a non-U.S. proposal with significant U.S. participation be selected, NASA's Office of External Relations will arrange with the foreign sponsoring agency or funding institution for the proposed participation on a non-exchange-of-funds basis, in which NASA and the non-U.S. sponsoring agency or funding institution will each bear the cost of discharging their respective responsibilities.

Depending on the nature and extent of the proposed cooperation, this arrangement may entail:

(1) a letter of notification by NASA;
(2) an exchange of letters between NASA and the sponsoring foreign governmental agency; or
(3) a formal Agency-to-Agency Memorandum of Understanding (MOU).

Export Control Guidelines Applicable to Foreign Proposals and Proposals Including Foreign Participation.

Proposals including foreign participation must include a section discussing compliance with U.S. export laws and regulations, e.g., 22 CFR Parts 120-130 and 15 CFR Parts 730-774, as applicable to the circumstances surrounding the particular foreign participation. The discussion must describe in detail the proposed foreign participation and is to include, but not be limited to, whether or not the foreign participation may require the prospective proposer to obtain the prior approval of the Department of State or the Department of Commerce via a technical assistance agreement or an export license, or whether a license exemption/exception may apply. If prior approvals via licenses are necessary, discuss whether the license has been applied for or if not, the projected timing of the application and any implications for the schedule. Information regarding U.S. export regulations is available at http://www.pmdtc.org and http://www.bxa.doc.gov. Proposers are advised that under U.S. law and regulations, spacecraft and their specifically designed, modified, or configured systems, components, and parts are generally considered "Defense Articles" on the United States Munitions List and subject to the provisions of the International Traffic in Arms Regulations (ITAR), 22 CFR Parts 120-130.

(m) Cancellation of NRA. NASA reserves the right to make no awards under this NRA and to cancel this NRA. NASA assumes no liability for canceling the NRA or for anyone's failure to receive actual notice of cancellation.

CERTIFICATION REGARDING DEBARMENT, SUSPENSION, AND OTHER RESPONSIBILITY MATTERS

PRIMARY COVERED TRANSACTIONS

This certification is required by the regulations implementing Executive Order 12549, Debarment and Suspension, 14 CFR Part 1269.

A. The applicant certifies that it and its principals:

(a) Are not presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal department or agency;

(b) Have not within a three-year period preceding this application been convicted or had a civil judgment rendered against them for commission of fraud or a criminal offense in connection with obtaining, attempting to obtain, or performing a public (Federal, State, or Local) transaction or contract under a public transaction; violation of Federal or State antitrust statutes or commission of embezzlement, theft, forgery, bribery, falsification or destruction of records, making false statements, or receiving stolen property;

(c) Are not presently indicted for or otherwise criminally or civilly charged by a government entity (Federal, State, or Local) with commission of any of the offenses enumerated in paragraph A.(b) of this certification; and

(d) Have not within a three-year period preceding this application/proposal had one or more public transactions (Federal, State, or Local) terminated for cause or default; and

B. Where the applicant is unable to certify to any of the statements in this certification, he or she shall attach an explanation to this application.

C. Certification Regarding Debarment, Suspension, Ineligibility and Voluntary Exclusion - Lowered Tier Covered Transactions (Subgrants or Subcontracts)

a) The prospective lower tier participant certifies, by submission of this proposal, that neither it nor its principles is presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from participation in this transaction by any federal department of agency.

b) Where the prospective lower tier participant is unable to certify to any of the statements in this certification, such prospective participant shall attach an explanation to this proposal.

This page has been included for your information.

CERTIFICATION REGARDING LOBBYING

As required by S 1352 Title 31 of the U.S. Code for persons entering into a grant or cooperative agreement over $100,000, the applicant certifies that:

(a) No Federal appropriated funds have been paid or will be paid by or on behalf of the undersigned, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, in connection with making of any Federal grant, the entering into of any cooperative, and the extension, continuation, renewal, amendment, or modification of any Federal grant or cooperative agreement;

(b) If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or attempting an officer or employee of any agency, Member of Congress, an or an employee of a Member of Congress in connection with this Federal grant or cooperative agreement, the undersigned shall complete Standard Form - LLL, "Disclosure Form to Report Lobbying," in accordance with its instructions.

(c) The undersigned shall require that the language of this certification be included in the award documents for all subawards at all tiers (including subgrants, contracts under grants and cooperative agreements, and subcontracts), and that all subrecipients shall certify and disclose accordingly.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by S1352, title 31, U.S. Code. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

This page has been included for your information.

CERTIFICATION OF COMPLIANCE WITH THE NASA REGULATIONS PURSUANT TO NONDISCRIMINATION IN FEDERALLY ASSISTED PROGRAMS

The (Institution, corporation, firm, or other organization on whose behalf this assurance is signed, hereinafter called "Applicant") hereby agrees that it will comply with Title VI of the Civil Rights Act of 1964 (P.L. 88-352), Title IX of the Education Amendments of 1962 (20 U.S. 1680 et seq.), Section 504 of the Rehabilitation Act of 1973, as amended (29 U.S. 794), and the Age Discrimination Act of 1975 (42 U.S. 16101 et seq.), and all requirements imposed by or pursuant to the Regulation of the National Aeronautics and Space Administration (14 CFR Part 1250) (hereinafter called "NASA") issued pursuant to these laws, to the end that in accordance with these laws and regulations, no person in the United States shall, on the basis of race, color, national origin, sex, handicapped condition, or age be excluded from participating in, be denied the benefits of, or be otherwise subjected to discrimination under any program or activity for which the Applicant receives federal financial assistance from NASA; and hereby give assurance that it will immediately take any measure necessary to effectuate this agreement.

If any real property or structure thereon is provided or improved with the aid of federal financial assistance extended to the Applicant by NASA, this assurance shall obligate the Applicant, or in the case of any transfer of such property, any transferee, for the period during which the real property or structure is used for a purpose for which the federal financial assistance is extended or for another purpose involving the provision of similar services or benefits. If any personal property is so provided, this assurance shall obligate the Applicant for the period during which the federal financial assistance is extended to it by NASA.

This assurance is given in consideration of and for the purpose of obtaining any and all federal grants, loans, contracts, property, discounts, or other federal financial assistance extended after the date hereof to the Applicant by NASA, including installment payments after such date on account of applications for federal financial assistance which were approved before such date. The Applicant recognized and agrees that such federal financial assistance will be extended in reliance on the representations and agreements made in this assurance, and the United States shall have the right to seek judicial enforcement of this assurance. His assurance is binding on the Applicant, its successors, transferees, and assignees, and the person or persons whose signatures appear below are authorized to sign on behalf of the Applicant.

This page has been included for your information.